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## Original Communications

### A CORRELATION OF ENDOMETRIAL HISTOLOGY WITH CLINICAL SYMPTOMS*

LYMAN W. MASON, M.D., WILLIAM C. BLACK, M.D., AND REUBEN G. GUSTAVSON, PH.D., DENVER, COLO.

IN 1931 we began a study which had for its object the possible correlation of endometrial histology at varying times during the menstrual cycle with estrin concentration, as determined by its extraction from the urine. Daily twenty-four-hour urine specimens were extracted for estrin through one, two, or more menstrual cycles. For several years endometrium specimens were obtained immediately following a menstrual period, at the midinterval, and immediately before menstruation on each patient studied. In a number of cases, specimens were obtained weekly.

It was finally concluded that, as the study was being conducted, no such correlation as was originally thought possible could be shown, and as for obvious reasons daily endometrium specimens could not be obtained over long periods of time, the original purpose of the study was abandoned. Instead, the estrin study was continued separately, and has been reported in another paper. As increasing numbers of endometriums were examined microscopically, a definite correlation of endometrial histology with the clinical aspects of various menstrual phenomena became more and more apparent.

Endometrium specimens have been obtained from over 50 cases, comprising practically the entire range of menstrual phenomena from those

*From the private practice of L. W. M., the Department of Pathology, University of Colorado School of Medicine and Hospitals, and The Research Laboratories, University of Denver.

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entirely normal to those in which uterine bleeding was continuous over a considerable period of time.

We construe as normal those women whose menstrual periods are regular at twenty-eight-day intervals, or close to this, who flow from four to six days moderately, and whose periods are painless. In addition, we have limited our concepts of normal to those women who have had one or more children, in whom pregnancy occurred without undue lapse of time. In the final analysis, the ability to conceive and bear children is our only incontrovertible proof of sexual normality. The abnormal cases represent the usual range of menstrual abnormalities which bring these patients to the gynecologist. All the cases studied were the private patients of one of us (L. W. M.) so that accurate histories and adequate examinations and follow-up were possible.

With few exceptions, all the endometrium specimens were obtained in the office. In these, no anesthetic, local, or otherwise, was used. Specimens were obtained with a very small sharp curette which could in most instances be introduced through the cervix without dilatation. Occasionally, in nulliparas or virgins, slight dilatation of the cervical canal with the smallest Jolly dilator was necessary. We prefer a curette for this purpose to a punch of any sort, since many times we noted the interesting fact that the glandular changes differed considerably in various parts of the endometrium.

The curette is introduced gently through the cervix, carried to the fundus and brought down to the cervix in the positions of 12, 3, 6, and 9 o'clock. Comprehensive samples of endometrium are thus obtained. Sometimes the specimen is obtained by bringing the curette down in a spiral motion from the fundus to the cervix. With proper gentleness, the complaint of cramping pain is minimal, and no patient ever refused further specimens when requested. In no instance was there the slightest deleterious effect, either during the procedure or after.

As stated previously, for several years specimens were obtained at least three times a month, viz., immediately after a menstrual period, at midinterval, and immediately preceding menstruation. However, it was finally definitely concluded that as much could be learned from one specimen, obtained immediately before a menstrual period, as from three or more, and for the past several years, all specimens have been obtained at this time. When uterine bleeding is continuous, it probably makes no difference when they are obtained. From an immediate premenstrual specimen, a complete history of the hormone action on the endometrium since the preceding menstruation can be read, and other specimens obtained during that time are superfluous.

In the interpretation of the accompanying photomicrographs, it is in order to review briefly the present working theories concerning the physiology of menstruation.

During menstruation, most of the endometrium is desquamated, and immediately following, it is represented in sections by a stroma in which can be seen rather widely spaced uterine glands. These are small and compact, and are lined by a single layer of low cuboidal cells. During the period of follicle growth, the endometrium proliferates. This is marked by a greatly increased vascularity and thickness of the endometrium, and a hypertrophy and hyperplasia of the uterine glands, the cells becoming columnar in type. Following ovulation, which occurs sometime around midinterval, the corpus luteum develops. The hyperplasia of the glands continues, and in addition, becoming noticeable several days before menstruation begins, the glands take on distinct secretory characteristics, which are evidenced in the histologic appearance of the glands by vacuolization of the gland cells, with a charac-

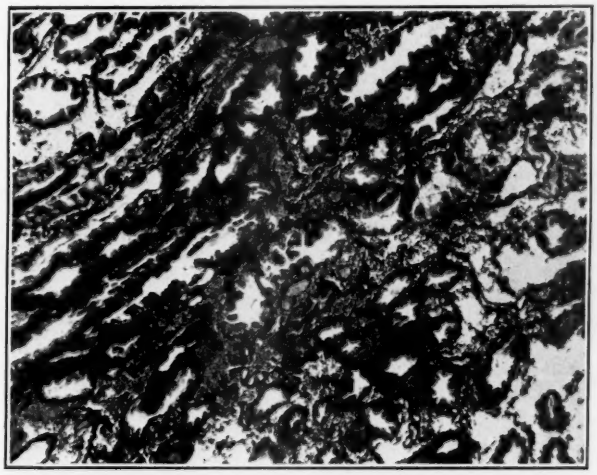

Fig. 1.—M., aged thirty-one years. Entirely normal menstrual history. No dysmenorrhea. Now normally pregnant at eight months.

teristic "fuzziness" of the gland borders. At this time, the lumina are more or less filled with a mucoid material.

The characteristic hormone of the follicle is estrin, and it is under its influence that the glandular hyperplasia occurs, while the characteristic hormone of the corpus luteum is progesterone, which is responsible for the secretory changes which occur premenstrually in the glands. However, estrin is secreted by the corpus luteum also, in even greater amounts than by the follicle. The function of progesterone seems to be to prepare the endometrium for the nidation of the fertilized ovum. Its full and complete action also seems to be necessary for normal menstruation, i.e., for menstrual periods which begin and end sharply, which last for a normal length of time with moderate flow, and which are free from pain. We have not found a premenstrual endometrium which we considered normal in any patient whose menstrual periods did not fulfill these requirements.

A normal female sex cycle, therefore, is predicated upon the normal activity of these two ovarian hormones, estrin and progesterone. They must be elaborated in adequate amounts, and there must be a normal balance between them. In the light of our present knowledge, this is

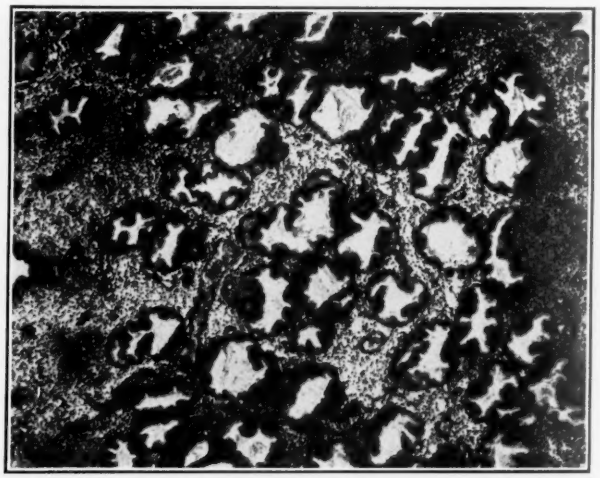

Fig. 2.—K. B., aged forty years. Entirely normal menstrual history. Never any dysmenorrhea. Three normal pregnancies, the last three years ago.

Fig. 3.—D. B., aged twenty years. Entirely normal menstrual history. Never any dysmenorrhea. Now normally pregnant at five months.

in turn dependent upon the proper functioning of the sex hormone or hormones of the anterior hypophysis, which act, although possibly not entirely, through the ovary. While not yet proved, it makes the matter somewhat easier to understand if we follow the postulation of two hypophyseal sex hormones, the follicle stimulating hormone and the luteinizing hormone. The first of these stimulates the development of the

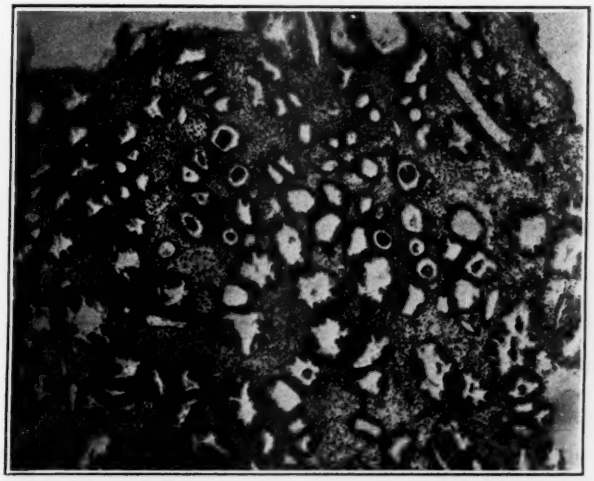

Fig. 4.—G. O., aged twenty-one years. History of previous pelvic infection, probably gonorrheal. Alternating menstrual periods of four and nine days' duration. Intervals normal. Flow not excessive in either case. Specimen taken just before an expected nine-day menstruation. Decreased secretory activity of the glands is apparent. Operation was done, at which time both tubes (abscessed) and right ovary, which was imbedded in scar tissue and polycystic, were removed. Following this, periods were all of four days' duration, painless and with moderate flow. Evidently the alternating nine-day periods were controlled by the diseased right ovary. Unfortunately, it was impossible to obtain a subsequent endometrium specimen. We believe it would have been normal.

Fig. 5.—I. M., aged twenty-six years. Normal menstrual history. One normal pregnancy shortly after marriage. No pregnancies for five years. Then followed 2 spontaneous abortions at an interval of a year. Next pregnancy continued after a threatened abortion at two months. From this time until term, patient was treated continuously with pregnancy urine extracts. Baby normal. One and one-half years later there was another pregnancy. No treatment was given during this pregnancy, which ended in a miscarriage at six months.

This endometrium shows considerable diminution of progesterone influence, reflected in a decreased secretory activity of the glands. Menstruation and/or fertility are probably never normal in an individual who shows this much hormonal imbalance.

follicle with its elaboration of estrin, and both, but particularly the latter, are responsible for the development of the corpus luteum and its particular hormone progesterone.

Figs. 1, 2, and 3 are photomicrographs which represent what we consider normal endometriums. There is a normal hyperplasia of the

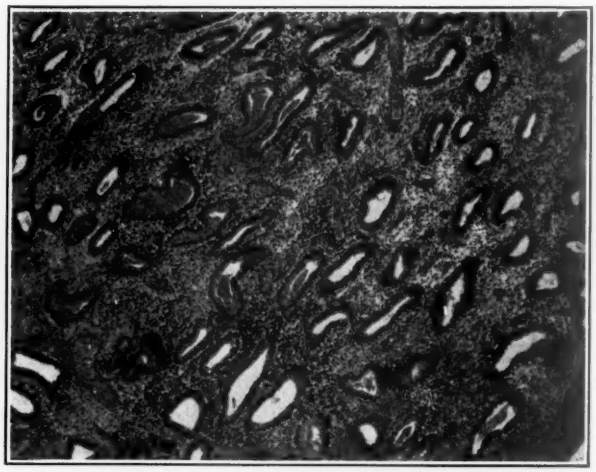

Fig. 6.—B., aged twenty-four years. This patient's periods were regular, but the duration was from eight to twelve days. Flow was quite excessive. Patient was in a sanitarium in Denver with an active tuberculosis. That the tuberculosis was probably not a factor in the menstrual abnormality, note the following section: This section shows a normal, or even an increased, glandular hyperplasia, but the progesterone influence is slight, reflected in almost absent secretory characteristics in the glands.

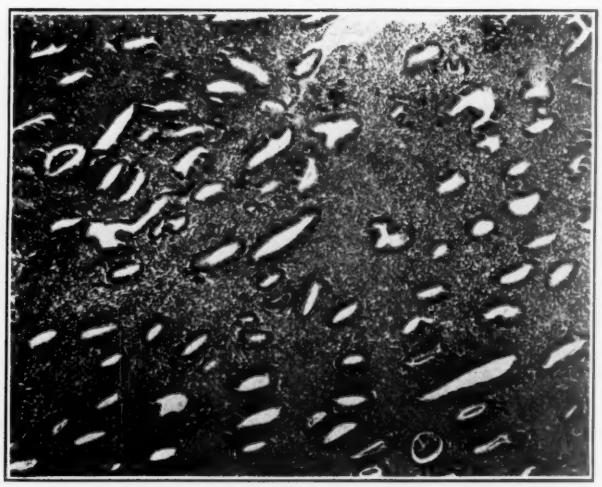

Fig. 7.—F. M., aged thirty-three years. Symptoms in this case were almost identical with those of the preceding one, i.e., regular menstrual intervals, but flow was prolonged and quite excessive. There have been times when the hemoglobin has fallen from 90 per cent to 55 per cent during a single menstruation. Patient is married and has two children, the youngest five years of age. Since that time there has been a spontaneous abortion at two and one-half months.

As noted, this patient's symptoms are practically identical with those of the preceding patient, and their endometriums are practically identical.

glands, and they show well the normal premenstrual secretory characteristics, as evidenced by the "fuzzy" appearance of their inner borders. An endometrium of this type presupposes a normal follicle development with rupture and the development of a normal corpus luteum. It also presupposes the extrusion of a normal ovum when the follicle ruptures, but this may not necessarily be so, nor has it been proved as yet. From the hormone standpoint, an endometrium of this kind can only result when there has been a normal elaboration of estrin by the follicle, and of estrin and progesterone by the corpus luteum, and of a normal balance of activity between them.

At the other end of the series we find the familiar and typical "Swiss cheese" pattern of endometrium, which is believed to result from a long continued excessive action of estrin, and an absence of that of progesterone. In this type of endometrium, the hormone balance is completely destroyed. In conjunction with such endometriums, one finds ovaries which are polycystic, resulting from derangements in follicle maturity and rupture, and in which signs of current corpus luteum activity are absent. This is the type of nongravid endometrium with which the pathologist is most familiar for the reason that curettages are not usually done in the great number of patients whose menstrual abnormalities are of lesser extent than the continuous bleeding which nearly always results from such endometriums. We have not found such endometriums except in women in or at the menopause, and it is in these that a curettage is of paramount importance for diagnostic purposes.

We present a series of endometriums which fall in between the normals at the one end and the "Swiss cheese" type at the other, in which the departure from normal of each shades into an increasing departure from normal of the next. The patients' menstrual symptomology shows a similar gradation in severity, which can be correlated with the endometrial picture. It was of the greatest interest to us in examining a new specimen to observe how similar it always was to a former one from a patient with similar menstrual complaints and symptoms. The photomicrographs which follow are arranged in this series, and the salient points in the history of each case are presented.

It is evident that these endometriums grade almost imperceptibly into each other in the extent of pathology or hormone imbalance involved. The most characteristic feature in each succeeding specimen is the evident gradually diminishing progesterone action on the endometrium. There may or may not be evidence of excessive or diminished estrin action. We have not found any endometrium in which we could interpret anything pointing to excessive progesterone influence. It is of interest that no endometriums such as those shown in Figs. 11, 12, and 13 were found except in women in or at the menopause. None which showed so marked a departure from normal were found in younger

women. With the exception of the endometriums of this type, all were obtained from women in the optimum child bearing age.

The gradation of clinical symptoms corresponding to the endometrial specimens may be listed as follows:

1. Normal. Menstrual periods regular at intervals of approximately twenty-eight days; duration of flow four to six days, in moderate amount; beginning and end of flow sharply delimited; no dysmenorrhea (Figs. 1, 2, 3).

Fig. 8*A*.

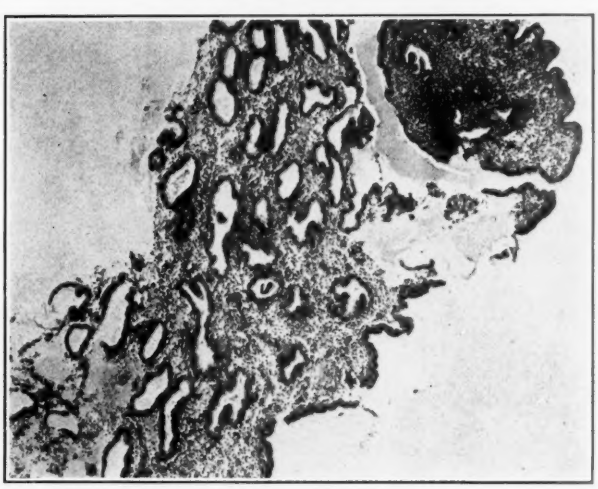

Fig. 8*B*.

**Fig. 8.—E. S.**, aged twenty-one years. These three specimens (*A*, *B*, and *C*) were obtained immediately preceding menstruation in three successive months. There was one normal pregnancy, which occurred shortly after marriage. Since that time extensive pelvic surgery has been done for salpingitis and adhesions. Both ovaries remain. Patient complained of gradually decreasing menstrual intervals with lengthening duration of flow. Flow rather scanty and "splotchy" in type.

It is interesting how alike these three specimens are. The glands are not normally hyperplastic. Secretory characteristics are slight. It is evident that not only is the progesterone influence defective, but that of estrin is also.

2. Normal intervals, but duration of flow is lengthened, and frequently amount is excessive. Flow may "dribble out" for several days at the end (Figs. 4, 6, 7).

3. Intervals still fairly regular, but duration of flow is considerably lengthened, sometimes for two weeks. Flow may vary from scanty to profuse several times during this period (Fig. 8).

4. Intervals irregular, with varying duration and amount of flow (Fig. 9).

5. Intervals usually irregular, and duration of flow lengthened so that one period almost lasts into the next one, but always some interval, of varying length, in which there is no bleeding (Fig. 10).

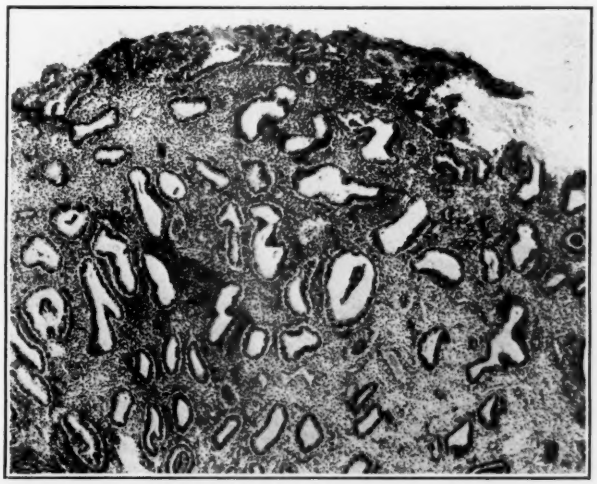

Fig. 8*C*.

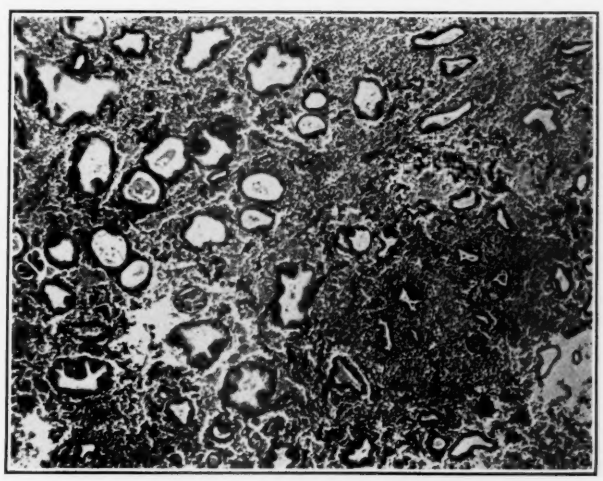

Fig. 9.—W. R., aged thirty-one years. This woman has had several pelvic operations. Her original complaint was dysmenorrhea. She still has considerable pain at times. There was one child, and pregnancy occurred shortly after marriage. For the past three years, periods have lasted for two weeks many times, and there is varying scanty flow and flooding in the same period. The right ovary has been removed because of "cysts." Pelvic examination is at present essentially negative, except that the remaining left ovary is quite small and hard. Both estrin and progesterone deficiency are more marked in this section than in the preceding one. The glands show less hyperplasia and less premenstrual changes. The stroma is thin and edematous.

6. Menstrual rhythm entirely lost and bleeding usually continuous (Figs. 11, 12, and 13).

It appears then, that menstrual abnormalities can be closely correlated with the histology of the endometrium, and that variations from normal here are due to an imbalance between the two ovarian hormones, estrin

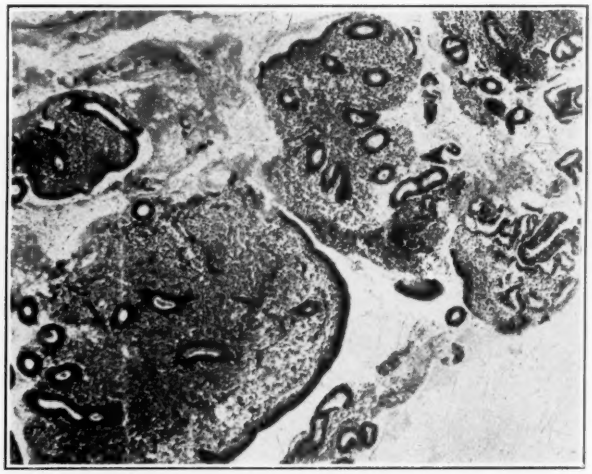

Fig. 10.—B. F., aged twenty-two years. For the first time in this series, we have the endometrium of a patient who occasionally flows from one menstrual period into the next. She is markedly overweight, and shows unmistakable evidence of pituitary deficiency. The section is the first which does not show in a single gland any evidence of progesterone activity. This specimen was taken about one hour after menstruation had begun. Estrin influence is greatly diminished also. Pelvis is grossly negative.

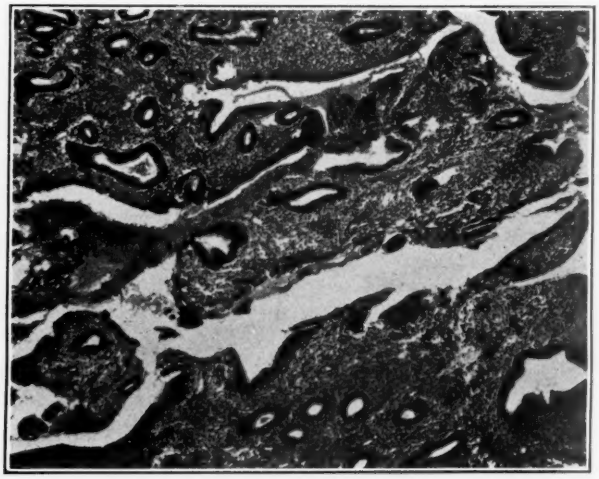

Fig. 11.—G. F., aged forty-three years. Specimen from a patient who had flowed continuously for two months. Menstrual periods were essentially normal until several months before, when they became irregular with increasing duration of flow. Endometrium was markedly thickened. This final marked departure from normal in the patient's symptoms was of relatively recent origin, and although the hyperplasia was marked, the glandular pattern shows only beginning cystic degeneration of the glands. No evidence whatever of corpus luteum activity.

and progesterone. The cause, in turn, of this imbalance may not lie in ovarian pathology per se, but may be due to abnormalities in the anterior lobe of the hypophysis, or even to pathology in other endocrine glands. In fact, we believe, so far as the female sex cycle is concerned, that a normal activity of, and balance between, all of the endocrine

Fig. 12.—E. G., aged forty years. The hormonal imbalance is still farther along in this case. In 1932, after a period of amenorrhea of three months' duration, during which time the patient thought herself pregnant, she began to flow excessively, and continued to do so until curettage was done three weeks later. Eighteen months later the same history repeated itself, and again twelve months later. The specimen shown was obtained after the second period of menorrhagia. The endometrium was so hyperplastic that it resembled pieces of placental tissue. Differing from the preceding specimen, in which only an occasional gland is dilated, in this one most of them are, and a considerable number are definitely cystic.

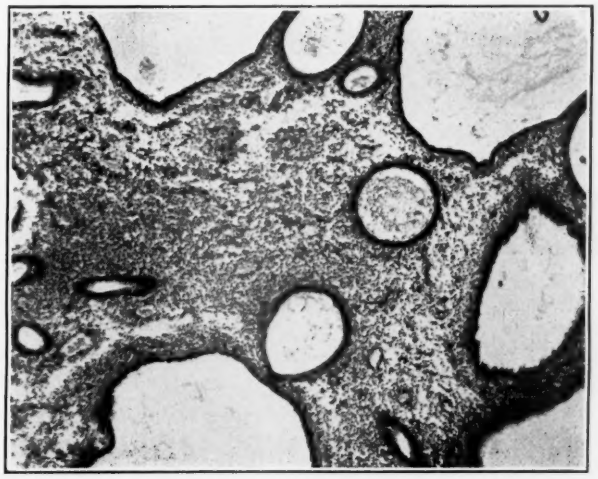

Fig. 13.—B., aged forty-one years. This patient has had menorrhagia for the past three years, and had been flowing continuously for the last seven months. Section shows enormous dilatation and cystic degeneration of the glands. This section represents the end histologic picture found in this type of case, i.e., constant uterine bleeding over long periods of time. It is the typical "Swiss cheese" pattern of endometrium.

glands is necessary to produce a premenstrual endometrium which we have described as normal.

As a result of our experience over a period of six years, we are of the opinion that the curettage of the nongravid uterus, of sufficient thoroughness to secure ample tissue for purposes of microscopic study, is a minor office procedure, and can be done with relative impunity. No anesthetic is necessary.

Without appending in detail the voluminous bibliography which would be necessary, we desire to acknowledge all of those workers in this and related fields who have contributed to our present knowledge of the physiology of the female sex cycle.

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## HEMORRHAGIC DISEASE OF THE NEWBORN

CARL T. JAVERT, M.D., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)*

THERE is a tendency in the newborn infant to bleed spontaneously from the mucous membranes during the first days of life. This condition has been termed: "idiopathic hemorrhage," "hemorrhagic diathesis," "hemophilia neonatorum," "umbilical hemorrhage," "melena neonatorum," "hemorrhagica neonatorum," and "hemorrhagic disease." The etiology remains obscure.

Hemorrhagic disease is either present at birth or occurs soon thereafter. The mortality is high unless human blood is promptly administered. Consequently, the accoucheur is responsible for its recognition and treatment. Stander has advocated that the total infantile mortality rate should include all deaths, regardless of cause, occurring in the first fourteen days of life. Therefore, a successful confinement entails the delivery of a "good baby," and one that remains so for fourteen days. For these reasons, the present study of hemorrhagic disease of the newborn was made, placing emphasis on obstetric and parturitional factors that appear to be contributory.

### HISTORICAL REVIEW

Omphalorrhagia was first described by Watts in 1753. Rilliet in 1848 commented on intestinal hemorrhage in newborn infants. In 1850, Bowditch pointed out the association of such bloody dejection with umbilical hemorrhage. He considered this syndrome to be very rare, since it was not mentioned in the leading medical texts and journals of that period. This caused Minot in 1852 to state that "during the past few years, numerous instances have been reported." Minot reiterated the contention of Bowditch that umbilical bleeding was a manifestation of a diathesis, with co-existing bleeding from the gums, stomach, and intestine.

Coale in 1852 described hemorrhagic disease as it is known today. He reported a case that bled from the stomach and anus, without umbilical bleeding. This report

remained unnoticed, for later in 1885, Thayer reported 5 cases of umbilical bleeding occurring in 24,533 infants, and commented on the associated hemorrhage from the stomach and bowels.

Townsend in 1894 clarified the situation by stating that it was a common error to think of hemorrhage only in relation to the umbilicus. He reported 50 cases in a series of 10,700 infants that had multiple hemorrhagic lesions. Umbilical bleeding was present in 18 cases. Townsend named this syndrome "hemorrhagic disease of the newborn."

During the past forty years other advances have been made. These will be mentioned in the discussion, together with etiologic references. The reader is referred to the publication of Von Reuss, and of Schloss and Commiskey, for additional etiologic information.

## THE PRESENT STUDY

This study has been conducted from the records of 11,303 mothers and their infants. The cases comprise the full-term and premature deliveries on the public indoor and outdoor services of the Woman's Clinic, covering the period from September, 1932 to April, 1936, inclusive. Of 8,019 infants born in the hospital, 62 developed hemorrhagic disease, while on the outdoor service (Berwind Free Maternity Clinic) only 10 cases occurred in 3,284 infants delivered, making a total of 72 cases. All but 5 of these infants were cared for by the Pediatric Service of the New York Hospital.

Control statistics are from two sources, unless otherwise stated:

1. The Annual Report of the New York Lying-In Hospital for 1935 based on 3,488 full term and premature deliveries.

2. A series of 1,870 consecutive deliveries in this clinic now being studied for another purpose by Pastore.

The author is aware of the fallacy of comparing a small group of cases with large control series. Nevertheless, the deductions obtained are of value as clues, to be confirmed or refuted by further observations. Follow-up studies on the infants beyond the neonatal period of fourteen days are not within the scope of this paper.

## MATERNAL STATISTICS

The records of the 72 mothers whose infants developed hemorrhagic disease were reviewed as follows:

*Age.*—The average maternal age was 30.0 years, which is above the age reported by Peckham and Kuder of 23.8 years. The primiparas averaged 25.7 years, and the multiparas 34.0 years. This forecasts prolonged labor, and an increased tendency towards obstetric abnormalities.

*Race.*—There were 16 cases or 22.2 per cent in the black race, while the clinic registration is only 12.2 per cent. This indicates a tendency in a race of established debility. One Chinese infant developed the disease. Further racial differentiation was not conclusive.

*Parity.*—Primiparas contributed 35 or 48.6 per cent of the cases, with 52.2 per cent for the control. Multiparity was present in 37 or 51.4 per cent of the cases, with 48.7 per cent for the control. Multiparity is slightly increased, but is believed to have little direct significance.

*Complications of Pregnancy.*—Antepartum complications occurred in 45 or 62.5 per cent of the mothers, as compared with 22.3 per cent in the control. This difference of nearly 300 per cent is shown in Table I. The toxemias were grouped according to the classification in Stander's monograph. Sahli hemoglobin determina-

TABLE I. THE FREQUENCY OF ANTEPARTUM COMPLICATIONS OF PREGNANCY

| | | CASES | PER CENT | CONTROL |
|---|---|---|---|---|
| Anemia | (44 patients) | 16 | 36.3 | 4.0 |
| Toxemia | (72 patients) | 14 | 19.5 | 10.8 |
| Syphilis | (72 patients) | 6 | 8.3 | 3.0 |
| Other | (72 patients) | 9 | 12.5 | 4.5 |
| | | 45 | 62.5 | 22.3 |

tions in the last trimester of pregnancy averaged 65 per cent in 44 cases studied, of which 16 cases were below 70 per cent. Cardiac disease, pyelitis, and pulmonary tuberculosis constitute the group marked "other." The high incidence of the complications of pregnancy, together with the increased age and racial factors, make maternal debility a decided entity.

*Pelvis.*—Abnormal pelves were present in 10 or 13.8 per cent of the cases, which is higher than the control of 8.4 per cent. Therefore longer labors and more operative deliveries may be expected.

*Duration of Labor.*—The duration in primiparas was 24.3 hours, and 12.5 hours for the multiparas, in the hospital cases; while on the outdoor service, all cases being in multiparas with an average of 10.6 hours. The usual duration in primiparas is eighteen hours, and about twelve hours for multiparas. The prolonged labor in primiparas is significant since nearly half of the cases of hemorrhagic disease occurred in first-born infants. Labor exceeded twenty-four hours in 15 cases, with an average duration in these of forty-one hours. Unfortunately, information regarding the frequency and intensity of the uterine contractions was not available.

*Operative Incidence.*—Operative delivery including breech extraction, was performed in 16 or 22.2 per cent of the cases, the control being 15.7 per cent. They were: midforceps, 7; low forceps, 5; breech extraction, 2; cesarean section, 1; version, 1. The indications were: fetal distress, 3; prolonged second stage, 5; maternal exhaustion, 2; prolapsed cord, 1; persistent occiput posterior, 2.

*Premature Rupture of the Membranes.*—This occurred in 18 or 25.0 per cent of the cases, which coincides with the control of 25.8 per cent. "Dry labor" was apparently not a factor.

*Medical Induction and Rectal Analgesia.*—This form of quinine medication was administered to 39 or 62.9 per cent of the mothers delivered in the hospital, and is over 200 per cent more than the control, as shown in Table II. Perhaps longer labors increased the need for analgesia. The dosage of quinine given orally was 0.6 gm., usually followed by 0.3 gm. in one hour. The dosage of quinine given rectally was 1.3 gm. in 7 cases; and 0.6 gm. in 17 cases, the latter dosage was repeated in 5 cases. The average time interval between medication and delivery was 30.1 hours for the oral, and 10.8 hours for the rectal administration. No definite conclusions can be drawn regarding quinine as an etiologic factor, although quinine hemolysis has been reviewed by Terplan and Javert in early pregnancy.

*Other Drugs.*—Bismuth and arsphenamine were given to 5 mothers. The average dosage of bismuth was 0.1 to 0.3 gm.; arsphenamine 1.5 to 3.7 gm. Morphine and

TABLE II. THE USE OF QUININE IN 62 HOSPITAL CASES

| | CASES | PER CENT | CONTROL |
|---|---|---|---|
| Medical induction | 15 | 24.2 | 4.7 |
| Rectal ether | 24 | 38.7 | 22.2 |
| | 39 | 62.9 | 26.9 |

scopolamine, nembutal, codeine, aspirin, pyramidon, were used in a small number of cases. Ten mothers received iron therapy.

*Anesthesia.*—The effect of anesthesia has been tabulated in Table III. No anesthesia, nitrous oxide alone, and ether alone, seemed to produce more cases. When ether was added to the nitrous oxide, fewer cases occurred. This may be due to the addition of oxygen along with the ether, and supports the anoxemia theory as advocated by Graham.

TABLE III. THE EFFECTS OF ANESTHESIA

| | CASES | PER CENT | CONTROL |
|---|---|---|---|
| No anesthesia | 14 | 19.4 | 4.7 |
| Nitrous oxide | 19 | 26.3 | 16.0 |
| Ether alone | 6 | 8.3 | 3.4 |
| Nitrous oxide, *oxygen,* ether | 33 | 45.8 | 75.5 |
| | 72 | | |

*Placenta.*—The average weight was 667 gm., which is normal. Only 8 or 11.1 per cent of the placentas were abnormal. This is lower than the figure of 18.0 per cent reported by Traut. The abnormalities included: placentitis 3, endarteritis, circumvallation, blood cysts, fibrinoid degeneration, hemochromal degeneration 1 case each. There was suggestive evidence of placental syphilis in only 1 case.

*Blood Loss in Third Stage of Labor.*—The blood loss in the cases measured by the Pastore apparatus averaged 371 c.c., which was 100 c.c. greater than the control. In this group postpartum hemorrhage (600 c.c. or more) was 265 per cent more frequent. This increase was also noted in the estimated cases, and is shown in Table

TABLE IV. THE BLOOD LOSS IN THE THIRD STAGE

| | CASES | AVERAGE LOSS | CONTROL LOSS | POSTPARTUM HEMORRHAGE CASES | PER CENT | CONTROL |
|---|---|---|---|---|---|---|
| Measured | 32 | 371 c.c. | 271 c.c. | 6 | 18.8 | 7.1 |
| Estimated | 40 | 320 c.c. | | 3 | 7.5 | 3.2 |
| | 72 | | | | | |

IV. The increased incidence of postpartum hemorrhage was apparently due to the greater frequency of anesthesia, analgesia, operative delivery, prolonged labor, etc., which, according to Pastore, tend to produce excessive blood loss. Perhaps these factors, which cause increased bleeding in the mothers, may also influence the infants to bleed abnormally.

*Maternal Morbidity and Mortality.*—Temperatures were taken every four hours. Two rises above 38° C., on two successive days not including the first twenty-four hours, constitutes a febrile puerperium. This was present in 16 or 22.2 per cent of the cases, with 10.6 per cent in the control series. This increased morbidity is to be expected, because of the larger number of operative deliveries and the greater incidence of postpartum hemorrhage as well as increased maternal debility. There was one maternal death due to peritonitis.

*Drugs Used Postpartum.*—Pituitrin and ergot preparations were both given to practically all of the patients. No definite conclusions can be made, since the transmission of these drugs to the infant through the colostrum in sufficient amounts has not been established.

## INFANT STATISTICS

The records of the 72 infants born to the mothers presented above were analyzed as follows:

*Incidence.*—Of the 8,019 infants born in the hospital, 62 developed hemorrhagic disease, giving an incidence of 0.773 per cent. On the outdoor service, 10 of the 3,284 infants developed the disease, or 0.304 per cent. A comparison with Townsend's figures is given in Table V. That the incidence is over 100 per cent greater in the hospital-born babies deserves investigation. The lower incidence on the outdoor service was not due to failure in recognizing the cases, since the same obstetric staff supervised both services.

TABLE V. THE INCIDENCE OF HEMORRHAGIC DISEASE

| | INDOOR SERVICE | | | | OUTDOOR SERVICE | | |
|---|---|---|---|---|---|---|---|
| | NO. OF CASES | YEAR | CASES | INCIDENCE | NO. OF CASES | CASES | INCIDENCE |
| New York Hospital | 8,019 | 1936 | 62 | 0.773% | 3,284 | 10 | 0.304% |
| Boston Lying-In | 6,700 | 1894 | 46 | 0.67 | 4,000 | 4 | 0.10 |

*Heredity.*—Nothing definite can be said. Only 4 of the mothers returned for subsequent delivery and all had normal infants. Minot and Kugelmass have pointed out the occurrence in successive pregnancies.

*Sex.*—Males were affected in 49 or 68.0 per cent of the cases. Townsend, Capon, and Dembo found the sexes about equal.

*Birth Weight.*—The average weight was 3380 gm. (7.5 pounds), the control weight being 3,427 gm.

*Duration of Gestation.*—Using the duration of 280 days as normal, the average duration of pregnancy was 275 days; 40 infants, or 55.5 per cent, had a duration of 264 days, and these averaged 3,048 gm. in weight. This indicates a definite tendency toward immaturity, which was also shown by the increased incidence of premature infants.

*Prematurity.*—Seven or 9.7 per cent of the infants weighed less than 2,500 gm., while the clinic incidence of prematurity is only 2.0 per cent. This shows a decided preponderance of premature infants. All infants weighing less than 2,500 gm. and under 45 cm. in length are considered prematures. Babies weighing less than 1,500 gm. were excluded.

*Weight Loss.*—The average initial loss was 257 gm. which agrees with the figure of 250 gm. given by Williams.

*Infant Feeding.*—This was routine and did not appear to be a factor.

*Pyrexia.*—Temperature above 37° C. was present in 14 or 19.4 per cent of the cases; of these 5 had bronchopneumonia. Townsend found fever in nearly all of his cases. Tyson found fever in 14 per cent of newborn infants, the chief causes being inanition and dehydration.

*Rash.*—Dermatitis was present in 23 cases. The routine use of ammoniated mercury reduces the value of this observation. However, a drug eruption (quinine, ergot) may have produced some of these reactions.

*Jaundice.*—This was present in 15 or 20.8 per cent of the cases and is in agreement with the figure of 20 per cent quoted from DeLee.

*Syphilis.*—The serology, x-ray of long bones, autopsy, or placental sections, did not definitely reveal the presence of congenital syphilis in the infants born to mothers with positive serology, although there was suggestive evidence in 2 cases. However, Mracek found that 14 per cent of 132 cases of congenital syphilis had hemorrhagic lesions.

*Resuscitation.*—The necessity for the use of the Flagg technique is a fairly accurate index of asphyxia; it was used in 7 or 11.2 per cent of the hospital cases. McGrath and Kuder found that it was used in 3.0 per cent of the infants born in the clinic. The increase may be due to the greater number of premature infants, operative deliveries, longer labors, anesthesia and analgesia. Whatever the causes may be, the fact remains that anoxemia resulted, requiring resuscitation.

*Source of Hemorrhage.*—The clinical observations are presented in Table VI. Over half of the infants had two or more lesions. The multiplicity indicates the generalized manifestations of the process, which is corroborated by autopsy (see Table X).

TABLE VI. THE SOURCES OF HEMORRHAGE IN THE INFANTS

| | | | | | |
|---|---|---|---|---|---|
| Emesis | 31 | Cord | 7 | Mouth | 3 |
| Melena | 12 | Foreskin | 6 | Urine | 2 |
| Petechiae | 7 | Vagina | 6 | Eyes | 2 |

*Time of Onset of Bleeding.*—More than one-third of the infants developed bleeding within the first day of life, as shown in Table VII. For each succeeding day there is a progressive decline in the number of cases that begin to bleed. For practical purposes, it can be said that bleeding does not occur after the first week of life. Diamond states that bleeding usually occurs between the third and sixth days of life.

TABLE VII. BLEEDING ACCORDING TO DAY OF ONSET

| | CASES | PER CENT |
|---|---|---|
| First day | 25 | 34.7 |
| Second day | 14 | 19.5 |
| Third day | 13 | 18.1 |
| Fourth day | 9 | 12.5 |
| Fifth day | 5 | 6.9 |
| Sixth day | 4 | 5.5 |
| 7th day and over | 2 | 2.8 |

*Bleeding Time.*—The Duke method was done in 38 cases, with an average of 14.2 minutes. Rodda states that four minutes is normal. The majority of the cases had normal bleeding times. However 11 were definitely prolonged with an average of 44.2 minutes.

*Clotting Time.*—The capillary tube method was used in 36 cases, with an average time of 9.7 minutes. Rodda gives seven or eight minutes as the maximum normal range. The majority of the cases were normal, while 10 cases were definitely prolonged with an average of 27.4 minutes. The infants with prolonged bleeding time invariably had a normal clotting time and vice versa. These determinations have a diagnostic value when prolonged, and serve to indicate the cases that are more severe.

*Blood Studies.*—Complete or partial studies were made in 41 cases, and they are summarized in Table VIII. The examinations were done on the day of onset of bleeding which corresponds to the day of life. There is no marked deviation from the control figures of Lucas for the first day of life. Of 15 infants studied on the first day, 3 had an average red cell count of 2,900,000, which if omitted from the average of the first day would increase the average count to 5,700,000. During

the first week of life, 7 additional cases of anemia were discovered, making a total of 10 cases out of 41, or 24.3 per cent, with anemia. Whether these were primary or due to the hemorrhagic process is conjectural.

The increased number of nucleated red cells is interpreted as evidence of prematurity although erythroblastosis should be considered. Parsons and Hawksley

TABLE VIII. BLOOD STUDIES ACCORDING TO DAY OF ONSET AND OF LIFE

| | RED COUNT | GM. HG | WHITE COUNT | PLATELETS | DIFFERENTIAL COUNT | |
|---|---|---|---|---|---|---|
| | | | | | LYMPHS | NORMOBLASTS |
| First day | 5,200,000 (13) | 20.8 (12) | 18,100 (11) | 162,000 (7) | 30 | 13.0 (10) |
| Second day | 5,200,000 (13) | 21.6 (11) | 16,000 (11) | 154,000 (9) | 33 | 2.5 (12) |
| Third day | 5,200,000 ( 6) | 21.0 ( 6) | 13,800 ( 7) | 290,000 (2) | 38 | 4.0 ( 6) |
| Fourth day | 4,900,000 ( 3) | 21.6 ( 3) | 9,800 ( 3) | 290,000 (2) | 39 | 0.0 ( 4) |
| Fifth day | 5,900,000 ( 3) | 22.2 ( 3) | 19,900 ( 3) | 200,000 (2) | 17 | 0.0 ( 2) |
| Control Lucas | 5,500,000 | | 19,900 | 305,000 | 20 | 1.0 |

(Figures in parentheses indicate number of cases studied)

state that the premature infant has nucleated red cells in direct proportion to the degree of prematurity. Terplan suggested that these cells can be enumerated in the fetal capillaries on histologic section of the placenta. This has been worked out by Ryerson and Sanes.

*Blood Grouping.*—All infants receiving transfusions were grouped and cross matched. The distribution of the groups was within the expected limits.

*Treatment.*—The type of therapy with results is presented in Table IX. The average amount of blood given by transfusion was 60 c.c.; citrated blood was used in all transfusions. The average amount of whole blood given intramuscularly was 18 c.c. A comparison of results with other investigators is given in the same table.

TABLE IX. THE TYPES OF TREATMENT

| | CASES | DEATHS | MORTALITY | CASES | MORTALITY | INVESTIGATOR |
|---|---|---|---|---|---|---|
| None | 8 | 4 | 50.0% | 46 | 84.0% | Minot |
| | | | | 50 | 62.5 | Townsend |
| Whole blood | 16 | 0 | 0.0 | 27 | 10.7 | Capon |
| Blood serum | 0 | | | 13 | 0.0 | Welch |
| Transfusion | 14 | 2 | 14.2 | 43 | 2.3 | Robertson |
| Whole blood and transfusion | 36 | 5 | 13.8 | 21 | 4.7 | Wing |

*Mortality.*—There were 11 deaths, giving an uncorrected rate of 15.7 per cent; while the clinic rate is 3.34 per cent. The mortality rate was highest when no human blood therapy was administered. Three infants weighing less than 2,000 gm. each are included. Of the 11 deaths, 10 occurred in the first week of life; 3 of these on the first day of life. During the period covered by this study, the total number of infantile deaths was 439, of which 11 or 2.5 per cent were caused by hemorrhagic disease.

*Causes of Death.*—Autopsies were performed on 10 of the 11 infants; all but 3 of these were done in the Department of Pathology. The chief pathologic findings comprised:

1. Bronchopneumonia 5 cases, one of which had gastrotomy.
2. Intracranial hemorrhage 3 cases; one was a 1,360 gm. infant with bilateral tentorial lacerations; one had an associated anemia with a hemoglobin of 35%; the last was suspected clinically but no autopsy was obtained.

3. Aspiration of amniotic fluid, 2 cases.
4. Not known, one case.

*Associated Pathology.*—The internal organs had multiple hemorrhagic lesions as shown in Table X. Many organs were also congested and hyperemic. If these lesions are correlated with the clinical evidence of bleeding, then hemorrhagic disease is a generalized systemic process. No gastric or intestinal ulcers were present. There was no evidence of syphilis. Congenital anomalies were found in 2 cases: atresia of the common bile duct and tracheo-esophageal fistula. Jaundice and anemia were noted in 2 cases each. Atelectasis was found in 4 cases. There was bloody fluid in the pericardial cavity in 4 cases, the pleural cavity in 2 cases, the peritoneal cavity in 1 case. Erythropoiesis was noted in the liver in 2 cases, in the spleen in 1 case. Blood cultures were not conclusive.

TABLE X. HEMORRHAGIC LESIONS IN THE INTERNAL ORGANS AT AUTOPSY

| LESION | ORGAN | CASES | ORGAN | CASES |
|---|---|---|---|---|
| Ecchymoses and Hemorrhages | Pericardium | 4 | Liver | 1 |
| | Pleura | 3 | Intestine | 2 |
| | Thyroid | 2 | Mesentery | 1 |
| | Thymus | 3 | Bladder | 1 |
| | Adrenal | 2 | Testicle | 2 |
| | Kidney | 2 | Mediastinum | 1 |
| | Tentorium | 2 | Subarachnoid | 1 |
| | Brain | 1 | Subdural | 1 |
| Hyperemia and Congestion | Lungs | 3 | Intestine | 2 |
| | Thyroid | 2 | Kidney | 2 |
| | Liver | 3 | Pancreas | 1 |
| | Spleen | 4 | Heart | 1 |

## DISCUSSION

This study has disclosed evidence indicating that hemorrhagic disease of the newborn is influenced by antenatal and intranatal factors. Previous authors have minimized the maternal aspects, i.e., Townsend and Capon, although Wing mentioned long hard labors as a predisposing factor.

The mothers in this series experienced abnormal pregnancies and labors. They were exposed to this by being older than the average childbearing woman. Labor was often long, hard, and difficult, as indicated by the prolongation of labor, the increased incidence of operative deliveries, and premature separation of the placenta in 2 cases. Abnormal pelves were also more prevalent. Information regarding the frequency and intensity of the uterine contractions was not available.

How does labor influence hemorrhagic disease? Physiologically, each uterine contraction forces blood from the placenta into the fetal circulation, raising the arterial and venous tension simultaneously. The elasticity of the vessels and capillaries permits considerable dilatation and distension. The resulting engorgement and congestion is a matter of degree. Should the forces of labor be unusually severe, then the separation of the capillary endothelial cells, or actual rhexis of the vessels, is to be expected. Blood then oozes into the tissues. This endothelial asthenia is more pronounced in immature infants whose circula-

tory apparatus is likewise immature, with incomplete elastic and connective tissue formation. The majority of the infants were more than two weeks from term, while 9.7 per cent were premature infants. Therefore immaturity and prematurity are definite factors in increasing the incidence of hemorrhagic disease.

The relationship to labor is further established by the fact that over one-third of the cases developed bleeding within the first twenty-four hours of life, while the rest showed signs of bleeding soon thereafter. Petechiae and hemorrhages should be looked for at the time of delivery. Often trauma to the ankles caused by holding the infant at this point, may produce the first petechiae to be visible. Clinically, and in the order of frequency, blood-tinged emesis, melena, skin petechiae, bleeding from the cord, were noted. At autopsy ecchymoses and petechiae were found in the internal organs in varying degree of severity. Every pathologist acquainted with autopsies on the newborn, has seen such hemorrhages even after a normal labor. However, since 34 per cent of the infants showed clinical bleeding on the first day of life, and since 3 infants died on the first day of life of hemorrhagic disease, and because hemorrhagic lesions are often encountered in infants at autopsy; it is more than probable that hemorrhagic disease runs part of its course intra-utero. The frequency of the pathologic lesions further suggests that many infants recover spontaneously, while others die with or without clinical evidence of bleeding. In the present series 4 cases, or 5.5 per cent, recovered without the benefit of therapy.

Intracranial hemorrhage has been found associated with these ecchymoses, and Green first pointed out that intracranial hemorrhage may be due to "dyscrasia hemorrhagica neonatorum." In 36 routine autopsies on newborn infants, Warwick found brain hemorrhages in 18; of these 8 had hemorrhagic disease. Dembo also noted 15 cases of intracranial hemorrhage in 55 cases of hemorrhagic disease. In our series, subarachnoidal, subdural, ventricular, and cerebral hemorrhages were present in 6 of the 10 cases at autopsy. Foote has stated that hemorrhagic disease may first manifest itself as intracranial hemorrhage.

Judging from the reports in the literature since 1850, when Bowditch pointed out the rareness of hemorrhagic disease, and West's failure to find a single case in 16,276 infants, this syndrome appears to be on the increase. Furthermore, the increase is more pronounced in hospital-born infants, with an incidence of 0.773 per cent as compared with 0.304 per cent on the outdoor service. The difference is partly due to the fact that all abnormal maternal cases were hospitalized. The outdoor service cases did not receive anesthesia, medical inductions or analgesia containing quinine. There were no primiparous mothers in the outdoor group, nor were any of the infants premature. The incidence on the outdoor service is greater than Townsend's figure of 0.10 per cent. This is attributed to the fact that 50 per cent of the outdoor cases were in the

colored race, and to the presence of debility of the mothers in the impoverished district which the Berwind Clinic serves. They had an average hemoglobin of only 69 per cent.

The more frequent use of drugs in the management of a confinement in the hospital seems to be important. Is the unknown toxin mentioned by Von Reuss as a cause of hemorrhagic disease actually a drug? A chronologic study of the use of drugs in obstetrics gives this view some support. Stearn in 1822 advocated ergot for the stimulation of labor. Its use was discontinued because of tetanic uterine contractions, and in 1875 Mullan recommended quinine instead. Watson in 1920 introduced castor oil, quinine, and pituitrin for stimulation of labor. Gwathmey in 1922 began the use of quinine and ether rectally as an obstetric analgesic. It is generally believed that quinine does not harm the mother or the infant. However, Gellhorn, Torland, and others have reported intrauterine deaths following the administration of quinine to the mother. In this series, quinine was given to 62.9 per cent of the mothers delivered in the hospital. No infantile deaths were attributed to the quinine.

Another group of drugs is bismuth and the arsenical preparations for the treatment of syphilis during pregnancy, which began in 1914 according to McKelvey. Antiluetic therapy was given to 5 mothers, 3 of whom were cared for on the outdoor service. Still another drug requiring consideration is ether, first introduced in 1847 by Simpson. It was administered either by inhalation or by rectum, or both, to a large number of the mothers. In addition many also received nitrous oxide. Webster in 1915 introduced this form of analgesia. Both have asphyxial properties. Ether has a dilating effect on the blood vessels. This relaxation allows more blood to enter the fetal circulation with each uterine contraction, resulting in engorgement and hyperemia. Did ether act in any way to produce the hemorrhagic lesions? An analogous drug, chloroform, was used by Graham with the production of hemorrhagic lesions in the unborn young of animals. Anoxemia was thought to have caused these ecchymoses. In our study, the addition of oxygen to nitrous oxide and ether anesthesia appeared to lower the incidence of hemorrhagic disease, whereas it was higher when nitrous oxide or ether was used alone. Further evidence of asphyxia is shown by the increased degree of resuscitation of the infants. Terplan believes that the hemorrhages noted in infants dying of asphyxia are produced by anoxemia.

The increased blood loss in the third stage may be further evidence of abnormal parturition. Many factors contributing to the increased blood loss were present. Postpartum hemorrhage was two and a half times more frequent, while the total average blood loss was 100 c.c. more than in the control. It can be inferred that some of the same factors causing excessive bleeding in the mothers probably influence the infants to bleed abnormally.

Dietary restrictions during the antenatal period and during parturition may precipitate a derangement in the prothrombin-antithrombin equilibrium, thereby affecting the coagulability not only of the mother's blood but also that of the infant. The treatment of toxemia of pregnancy by a low protein diet illustrates this view. Kugelmass raised the prothrombin values in the mother with a proper diet, and thereby was able to prevent hemorrhagic disease. Certainly the role of prothrombin merits investigation. Perhaps it is also a factor in postpartum hemorrhage. Moore and Brodie have reported a deficiency of vitamin B as a factor.

Whipple states that prothrombin and antithrombin are in delicate equilibrium, and that when antithrombin is in excess, purpura and bleeding are to be expected. In this series the average bleeding time was prolonged, and the clotting time was slightly above normal. One can conclude that abnormal clotting factors do not produce hemorrhages per se, but rather allow bleeding precipitated by the forces of labor to continue.

Howell's theory requires five factors. In hemorrhagic disease these are present as follows:

| | |
|---|---|
| Platelets | present, (Table V) |
| Calcium | normal (Lucas) |
| Prothrombin | low (Whipple, Lucas, Kugelmass) |
| Antithrombin | excessive (Howell, Kugelmass) |
| Fibrinogen | normal (Whipple) |

The derangement appears to be in the prothrombin-antithrombin balance. No studies were made to correlate this with the other clotting factors. However, an understanding of Howell's theory is essential, since it provides a clue which appears to be of value in the treatment of hemorrhagic disease. Whole blood or transfusion evidently supplies thromboplastin which neutralizes the excess of antithrombin according to Whipple. Prothrombin is then liberated and unites with calcium to form a clot around the traumatized blood vessels, and bleeding ceases.

The mothers exhibited a marked degree of debility since nearly two-thirds of them had an antepartum complication. This has not been recorded by previous writers. A greater frequency in colored women whose debility is generally recognized, was also seen. The average hemoglobin value was only 65 per cent. Poorer maternal health was further established by the greater incidence of postpartum morbidity.

In regards to the infants, prematurity was outstanding, with an incidence of 9.7 per cent. Immaturity was also frequently observed. The presence of nucleated red blood cells at birth, either on examination of a blood smear or on histologic section of the placenta, may be a better indication of prematurity even in apparently full-term infants. Several infants had an increased number of nucleated red blood cells. Losee has also found prematurity to be a factor in hemorrhagic disease. In this clinic McKee has shown that 4.5 per cent of 310 premature infants

developed clinical signs of hemorrhagic disease, whereas the incidence for full-term and premature infants is only 0.773 per cent.

Blood studies were not conclusive. The average bleeding time was prolonged to fourteen minutes while the clotting time was under ten minutes. After treatment of the disease circumcision was done during the second week of life in 7 of the cases. No increased bleeding was noticed. Apparently the bleeding tendency of infants during the first few days of life was known to the ancient Jews, for in St. Luke, Chapter II, verse 21, a definite period of time is given: ". . . and when eight days were accomplished for the circumcising of the child. . . ." Carr found that prolonged labor and operative deliveries did not increase the bleeding and clotting times. Lucas states that a clotting time of twenty to forty minutes can be present without hemorrhage. The blood platelets were present in adequate numbers. Several infants had an increased number of nucleated red cells. An anemia existed in nearly one-fourth of the infants. This was evidently a result of the bleeding in most of the cases. In others prematurity seemed to be the cause since primary anemia of the Ecklin type is a rarity. A hemolysin may be responsible for the anemia.

The sepsis theory of Epstein, Welch, and Townsend was not given credence in this study. Blood culture studies in our cases were not remarkable. Only 14 cases had fever, 5 of which had bronchopneumonia. Townsend noted fever in all but 2 of his 50 cases. In preaseptic days Von Reuss states that umbilical bleeding was a frequent symptom of sepsis.

Icterus was not more frequent, which is contrary to the findings of Keating, Minot, and Thayer, who explained the bleeding on accumulation of bile in the blood, thereby prolonging the bleeding time. Thayer found an absence or an impervious condition of the bile ducts in 32 per cent of his cases. In this series only one infant had an atresia of the common bile duct.

## DIAGNOSIS

Clinical evidence of bleeding in the newborn infant has been the single criterion for the diagnosis of hemorrhagic disease. This is not sufficient, since it is necessary to differentiate it from: hemophilia, congenital syphilis, icterus gravis, purpura, erythroblastosis fetalis, traumatic bleeding, and spurious hemorrhage. This study has revealed the importance of maternal factors, such as antepartum complications, maternal debility, drugs before and during labor, long or severe labors, and the increased blood loss during the third stage of labor. Petechiae of the skin may be noted at birth, and many cases show spontaneous hemorrhages on the first day of life. Multiple lesions are often present. The child is often premature, or if of average weight, it has signs of immaturity. Nucleated red blood cells in the blood smear or in the fetal capillaries of the placenta are interpreted as evidence of prematurity,

although erythroblastosis must be considered in the differential diagnosis. The presence of anemia, and the prolongation of the bleeding and clotting times are helpful when they are abnormal, although both were often within normal limits.

### TREATMENT

The curative value of human blood in hemorrhagic disease is almost a specific; the beneficial substance is not known. There is reason to believe that it is thromboplastin. Mortality ranges from 50 to 84 per cent if blood therapy is not instituted, as is shown in Table IX. The blood is given intramuscularly or by transfusion. Welch in 1910 introduced the use of intramuscular serum, and Lambert in 1908 was one of the first to use transfusions.

In this series, 50 infants received transfusions of citrated blood, while 13 were given two or more transfusions. In this group the mortality rate was 14.2 per cent. Whole blood alone in the supposedly less severe cases resulted in no deaths. When whole blood and transfusion were used the mortality was 13.8 per cent. However, the mortality rate is not an accurate index of treatment, since the main causes of death were bronchopneumonia and intracranial hemorrhage. No attempt was made to correct the mortality rate, and the role of hemorrhagic disease in these cases can only be inferred.

The mother's blood was used for all the intramuscular injections, and for 21 of the tranfusions. The mother is an undesirable donor. She is usually debilitated and anemic; she has often had a long or severe labor; has received drugs and anesthesia; and has usually sustained an increased blood loss in the third stage of labor. While the mother's blood evidently contains the curative agent, the concentration has been lowered by the physiologic hydremia of pregnancy as well as by the blood loss. In view of these facts the early puerperium (when these infants bleed) is an undesirable time to take blood from the mother to give to her infant.

Transfusion is not justified for all cases unless an anemia is present. To increase the intravascular tension at a time when capillary tissues have been injured by the forces of labor, does not seem logical and may cause the bleeding to continue. Over one-fourth of the cases required repeated transfusions. It is believed that the existing polycythemia and the congestion and hyperemia of the internal organs will not be enhanced by blood intravenously. Furthermore, the possibility of a co-existing intracranial hemorrhage in addition to the multiple lesions in the internal organs, makes transfusion undesirable unless an anemia or a markedly prolonged bleeding time makes it mandatory.

How then can these cases be treated adequately? The beneficial value of intramuscular blood has been shown in Table IX and in the publication of Capon. Welch has advocated blood serum and employed as much as 209 c.c. over a period of days. Many object to whole blood since the

blood lost by the infant is not replaced. This view is not tenable since most of the infants did not have an anemia. Pooled serum when available would be ideal, together with sedation and rest of the bleeding organs. Schloss and Commiskey treated nine cases with human blood intramuscularly with a cure in 7 cases.

Prophylactically, intramuscular whole blood may have value in infants that have had an abnormal parturitional course. Heffernan gave whole blood to 800 consecutive infants to determine its value in intracranial hemorrhage. In these, no cases of hemorrhagic disease were observed, whereas at least 6 cases should have occurred.

## SUMMARY

A study of 72 cases of hemorrhagic disease, occurring in 11,303 infants born during the period from September, 1932, to April, 1936, inclusive, has been presented. This comprises the material on the indoor and Outdoor Services of the Woman's Clinic of the New York Hospital. Emphasis has been placed on certain maternal and infantile factors. Criteria have been suggested for diagnosis. The treatment has been discussed and the autopsy data have been included.

Additional studies are indicated and should include: antepartum and intrapartum aspects of pregnancy; the use of drugs; further consideration of the blood loss in the third stage of labor; dietary factors; prematurity; blood studies, especially normoblastic determinations in the blood smears or in the fetal vessels of the placenta; blood pressure and blood volume determinations; capillary fragility tests; arterial oxygen; and the value of intramuscular whole blood.

## CONCLUSIONS

1. The incidence of hemorrhagic disease is 0.773 per cent in the hospital, and 0.304 per cent in the outdoor service.

2. Parturitional factors are: prolonged or severe labor, anesthesia and analgesia, and increased blood loss during the third stage of labor.

3. Maternal debility, antepartum complications, and age appear to have an influence.

4. The intrauterine origin of hemorrhagic disease is more than probable.

5. Increased circulatory tension caused by the forces of labor may produce a separation of the capillary endothelial cells or actual rhexis of smaller blood vessels, thereby producing the multiple hemorrhagic lesions in the various organs, as were noted both clinically and pathologically.

6. The multiplicity of the lesions suggests that the condition is a generalized systemic process.

7. One-third of the cases began to bleed during the first twenty-four hours of life; only 2 cases had the onset of bleeding after the first week of life.

8. Bleeding precipitated by vascular trauma probably continues when the clotting or bleeding mechanism is abnormal.

9. The fetal factors were: immaturity and prematurity, the need for resuscitation indicating anoxemia, and the prolongation of the bleeding time.

10. The use of the mother as a blood donor is open to criticism.

11. Sedation and rest of the bleeding organs and the administration of intramuscular blood are important. Transfusion is indicated when these measures fail, or in the presence of anemia.

12. The total fetal mortality statistics show that 2.5 per cent of 439 neonatal deaths were due to hemorrhagic disease.

13. The fetal vessels of the placenta offer an excellent opportunity of studying the fetal blood at the time of delivery.

14. The same factors which cause excessive bleeding in the mothers, probably predispose the infants to abnormal bleeding.

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525 East 68 Street

# THE RELATION OF LABOR TO INTRACRANIAL INJURY IN THE PREMATURE INFANT*

W. E. Studdiford, M.D., and H. P. Salter, M.D., New York, N. Y.
*(From the Obstetrical and Gynecological Service and the Laboratory of Pathology, Bellevue Hospital, and the Department of Obstetrics and Gynecology, New York University, College of Medicine)*

IN RECENT years a great deal of interest has been shown in injuries sustained by the fetus during labor and delivery. Most of the emphasis has been laid on the lesions sustained by the full-term infant and its relation to instrumental delivery and breech extraction. Less interest has been shown in the character, method of production, and prevention of injuries to the premature fetus. Berlind,[1] Galloway,[2] Capper,[3] and Clifford,[4, 5] have discussed the causes and prevention of these lesions. Hemsath[6] has described them but appears to be at a loss as to their causation.

The pathologic lesions found at autopsy have been described by one of us in a previous article.[7] The general character of these lesions is illustrated in Fig. 1, showing the dural lacerations and subdural hemorrhage which are found most commonly in the term infant. In addition microscopic hemorrhage may be found in the brain itself. Fig. 2 shows the lesions most characteristic of the premature which consist of diffuse subarachnoid hemorrhage, gross cerebral hemorrhage, and, in particular, subventricular hematomas. As we will show later there is no sharp division between these two groups since the premature infant past the thirty-fifth week commonly is found to have a combination of both types of lesion at autopsy.

The forces producing intracranial injury in the term infant are apparently much greater than those which cause injury in the premature.

Tables I and II show 20 cases of term infants coming to autopsy between July 1, 1933 and Feb. 28, 1936. It will be noted that in eleven cases the delivery was accomplished by midforceps operations and that in a majority of instances it was necessary to rotate the fetal head. On five occasions the injury occurred during breech deliveries. In one instance the fetus was delivered by version and breech extraction. In only three instances was an injury found after spontaneous labor. In two of these cases the labor was precipitate with strong uterine contractions. It is worthy of notice that in this series there was no case of intracranial injury following delivery with low forceps. It may be concluded that injuries in term infants are most likely to occur in difficult midforceps or high forceps deliveries commonly involving rotation of the fetal head or in breech extractions. A minority occur due to abnormally strong uterine forces. The cranial structures of the

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term infant appear to be able to withstand the forces of normal labor. It is important to note that on no occasion in this series among the term infants was the premature type of lesion found. Tables III, IV, V, and VI summarize the premature infants coming to autopsy during the same period of time. It should be

Fig. 1.—Intracranial injury in term infant, delivered by forceps. Laceration of tentorium. Subdural hemorrhage.

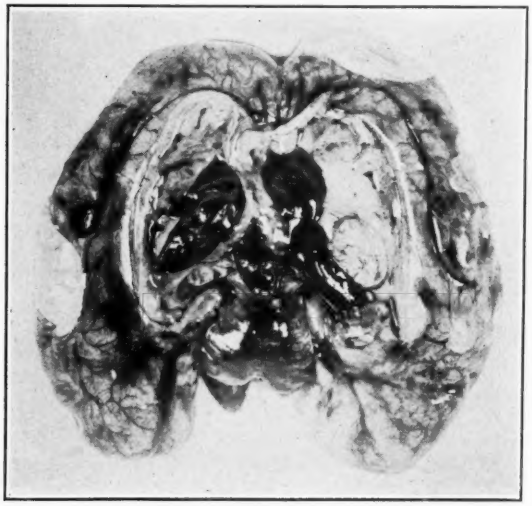

Fig. 2.—Intracranial injury in premature infant. Spontaneous delivery. Diffuse subarachnoid hemorrhage and bilateral subventricular hematoma.

stated clearly that in the estimation of prematurity, more weight was placed on the statement of the mother as to the duration of pregnancy than upon the weight or length of the infant. Pregnancies at or over the thirty-eighth week were considered to be at term. The prematures coming to autopsy were divided into two groups, those born between the thirty-fifth and thirty-eighth week of pregnancy,

TABLE I. TERM BABIES WITH HEAD INJURIES 20 CASES, JULY 1, 1933 TO FEB. 28, 1936

| NAME ACCESSION NUMBER | WEIGHT | DURAL LACERATION | SUBDURAL HEMORRHAGE | METHOD OF DELIVERY | AGE | APPEARANCE AT BIRTH | LENGTH OF GESTATION | LENGTH OF LABOR HOURS | DRY HOURS | PELVIS | PARITY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mrs. F.<br>19453 | 3390 | + | + | Breech | 5 min. | Poor | 40 | 3 | 25½ | Transverse contraction of outlet | Para 0<br>Grav. i |
| Mrs. L.<br>19571 | 2910 | + | + | Spontaneous | S/B | | 40 | 11½ | ½ | Ample | Para ii<br>Grav. iii |
| Mrs. M.<br>19702 | 3640 | + | + | Midforceps | S/B | | 40 | 68 | 68 | Ample | Para 0<br>Grav. i |
| Mrs. S.<br>20451 | 3196 | + | + | Barton midforceps R.O.T. | S/B | | 40 | 6½ | | | |
| Mrs. O.<br>20666 | 3310 | + | + | Precipitate with impacted shoulders | S/B | | 40 | 25 | 11 | Ample | Para ii<br>Grav. iv |
| Mrs. Mc.<br>20733 | 3064 | + | + | Breech | 6 min. | Poor | 40 | 21½ | 20 | Anthropoid | Para 0<br>Grav. i |
| Mrs. M.<br>22059 | 4100 | + | + | Midforceps<br>Kielland R.O.T. | S/B | | 40 | 16 | 2 | Gynecoid | Para 0<br>Grav. i |
| Mrs. M.<br>21415 | 3270 | + | + | Midforceps<br>Haig Ferguson<br>LOP—Toxemia | 3 days | | 40 | 26½ | 10 | Gynecoid | Para 0<br>Grav. i |
| Mrs. M.<br>21339 | 3190 | + | + | Spontaneous<br>Lac. of cervix.<br>Very strong pains | S/B | | 40 | 8½ | ½ | Gynecoid | Para v<br>Grav. vi |
| Mrs. S.<br>21243 | 3190 | + | + | Mid A<br>Kielland R.O.P. | S/B | | 40 | 1 | 15 | Gynecoid<br>Android tendency | Para 0<br>Grav. i |
| Mrs. F.<br>21091 | 4772 | + | + | Barton, high forceps L.O.T. | S/B | | 40 | 5 | 6½ | Android | Para viii<br>Grav. ix |
| Mrs. C.<br>20983 | 3190 | + | + | Version and breech after attempted high forceps R.O.T. | S/B | | 40 | 36 | 5 | Anthropoid | Para ii<br>Grav. iii |
| Mrs. M.<br>20944 | 3490 | + | + | Vertex R.O.P.<br>Kielland high forceps | S/B | | 40 | 18½ | 5 | Flat pelvis | Para 0<br>Grav. i |

TABLE II. TERM BABIES WITH HEAD INJURIES 20 CASES, JULY 1, 1933 TO FEB. 28, 1936

| NAME ACCESSION NUMBER | WEIGHT | DURAL LACERATION | SUBDURAL HEMORRHAGE | METHOD OF DELIVERY | AGE | APPEARANCE AT BIRTH | LENGTH OF GESTATION | LENGTH OF LABOR HOURS | DRY HOURS | PELVIS | PARITY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mrs. B.<br>21301 | 4432 | + | + | Midforceps<br>Kielland R.O.P. | S/B | | 40 | 33 | | Contracted outlet | Para 0<br>Grav. i |
| Mrs. P.<br>21447 | 3977 | + | + | Midforceps<br>Kielland R.O.P. | S/B | | 40 | 23 | 40 min. | Ample | Para 0<br>Grav. i |
| Mrs. R.<br>22218 | 2840 | + | + | Midforceps<br>Kielland L.O.T. | S/B | | 40 | 26 | 26 hr. | Android with poor outlet | Para 0<br>Grav. i |
| Mrs. B.<br>22237 | 2950 | + | + | Breech extraction.<br>Piper forceps | 10 hr. | Shock | 40 | 29 | 55 hr. | Gynecoid with poor outlet | Para 0<br>Grav. i |
| Mrs. M.<br>22349 | 4090 | + | + | Midforceps<br>Kielland R.O.P. | S/B | | 40 | 22 | 6 hr. | Gynecoid with android tendency and good outlet | Para 0<br>Grav. i |
| Mrs. M.<br>22312 | 2270 | + | + | Assisted breech | S/B | | 40 | 30 | 11½ hr. | Ample | Para ix<br>Grav. xii |
| Mrs. P.<br>22354 | 3065 | + | + | Breech extraction | S/B | | 40 | 15½ | 45 hr. | Gynecoid with good outlet | Para 0<br>Grav. i |

TABLE III. HEAD INJURIES IN BABIES THIRTY-FIVE WEEKS' GESTATION OR MORE, JULY 1, 1933 TO FEB. 28, 1936

| NAME ACCESSION NUMBER | WEIGHT | DURAL LACERATION | SUBDURAL HEMORRHAGE | SUBARACHNOID HEMORRHAGE | CEREBRAL AND VENTRICULAR HEMORRHAGE | METHOD OF DELIVERY | AGE | APPEARANCE AT BIRTH | GESTATION WEEKS | DURATION OF LABOR HOURS | DRY HOURS | PELVIS | PARITY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mrs. O.<br>19400 | 2355 | + | + | | | Precipitate in commode | 4 days | Fair | 36 | Precipitate | | Ample | Para ii<br>Grav. iii |
| Mrs. Z.<br>19671 | 2480 | + | + | | | Vertex spontaneous | 6 hr. | Cyanotic | 36 | 3 | 4 hr. | Ample | Para v<br>Grav. vi |
| Mrs. R.<br>19869 | 1950 | | | + | + | Vertex spontaneous | 7 days | Good | 35 | 27½ | 5 min. | Ample | Para i<br>Grav. ii |
| Mrs. C.<br>20058 | 1603 | + | + | + | | Vertex spontaneous | 9 hr. | Poor | 35 | 18 | 11 hr. | Ample | Para 0<br>Grav. i |
| Mrs. P.<br>20381 | 2468 | + | + | | | Version and breech | S/B | | 36 | 11 | 8 hr. | Ample | Para ii<br>Grav. iii |
| Mrs. N.<br>20794 | 2556 | | + | | | Spontaneous face | 5 days | Fair | 37 | 11 | 1 hr. | Normal | Para 0<br>Grav. i |
| Mrs. I.<br>22531 | 1800 | | | | + | Spontaneous vertex | 69 days | Good | 37 | 18 | 18 hr. | Died frank pneumonia<br>Porencephaly | |

and those born before the thirty-fifth week. Table III summarizes 7 cases belonging to the first group. It will be noted that the majority showed a lesion of the type generally found in term infants, while a minority showed the premature type of lesion. In the majority of infants the forces of labor were not noted to be abnormal and the delivery was spontaneous. One may conclude that in this group the fetal head has become large enough to be subject to compression when opposed to resistant soft parts but that the intracranial supporting structures have not yet developed sufficiently to resist these forces. The arachnoid and cerebral vascular lesions are noted in a minority of instances. It will be noted that the last case in this group died of pneumonia at the age of sixty-nine days. Evidence of old cerebral hemorrhage was found at autopsy. This suggests that the premature may survive cerebral vascular injury sustained at birth. It is possible that this type of lesion may give rise to neurologic signs and symptoms in later life. Tables IV, V, and VI summarize the autopsies and clinical histories of 38 premature infants and stillbirths. These are taken in sequence without regard to viability. It will be noted that the vast majority of these cases showed arachnoid or subventricular hemorrhages, the incidence of dural lacerations and subdural hemorrhage being markedly reduced in this group. The more premature the infant the greater was the likelihood of the former type of lesion. Thirty-two of these cases occurred following spontaneous vertex delivery. Five cases occurred after assisted breech deliveries and one followed a low forceps in which no episiotomy was done. It must be apparent from these summaries that the connective tissue supporting structures and the blood vessels in the premature infant are not always strong enough to resist the normal forces encountered during labor and delivery. This tendency becomes more marked the greater the degree of prematurity. Capper[3] believes that the vascular weakness depends on the lack of development of elastic tissue. Ylppo[8] has shown experimentally that the cutaneous vessels in the premature are abnormally fragile. Using suction on the skin he found that hemorrhages occurred with a negative pressure of 150 mm. of mercury whereas 520 mm. of mercury were required to produce the same effect in term infants.

Granting that we are dealing with a fetus with inadequate connective tissue and vascular development, it is of interest to speculate on the point during parturition at which these injuries occur. The dural lacerations are easily explained on the basis of compression, first, by the dilating cervix during the first stage and, second, by the opposition offered by the perineal structures during the second stage. One would expect that premature rupture of the membranes would be an additional factor since an intact amniotic sac tends to equalize intrauterine forces during the first stage. The exact cause of the vascular lesions is more difficult to determine. It must be supposed that the fetus is under a marked increase of pressure during the uterine contractions. The portion of the fetal head exposed in the dilating cervix or in the vaginal introitus becomes an area of relatively low pressure. In the second stage the expulsive forces are increased by the voluntary efforts of the patient. This pressure relationship is reflected to the intracranial structures. As a result the blood vessels in the area of relatively low pressure become distended. If distention is pronounced

TABLE IV. HEAD INJURIES IN BABIES UNDER THIRTY-FIVE WEEKS' GESTATION—38 CASES—JULY 1, 1933—FEB. 28, 1936

| NAME ACCESSION NUMBER | WEIGHT | DURAL LACERATION | SUBDURAL HEMORRHAGE | SUBARACHNOID HEMORRHAGE | CEREBRAL AND VENTRICULAR HEMORRHAGE | METHOD OF DELIVERY | AGE HOURS | APPEARANCE AT BIRTH | GESTATION WEEKS | DURATION OF LABOR HOURS | DRY HOURS | PELVIS | PARITY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mrs. G. 19939 | 1060 | + | + | | | Assisted breech | 12 | Poor | 30 | 8 | 0 | Not estimated | Para 0 Grav. i |
| Mrs. R. 19942 | 1021 | | | + | + | Assisted breech | 1 | Poor | 31 | 14 | 0 | Ample | Para i Grav. ii |
| Mrs. M. 19951 | 2383 | | | + | + | Spont. vertex | 2 | Fair | 32 | 21/4 | ? | Ample | Para iii Grav. v |
| Mrs. T. 20037 | 1580 | + | + | | | Breech | 8 | Poor | 26 | 7 | 2 | Not estimated | Para 0 Grav. i |
| Mrs. O. 20576 | 2043 | | + | + | + | Spont. vertex | 4 | Fair | 34 | 28 1/2 | 0 | Ample | Para 0 Grav. i |
| Mrs. G. 20584 | 1135 | | | + | + | Spont. vertex | 5 | Fair | 28 | 6 | 8 1/2 | Generally contracted | Para i Grav. ii |
| Mrs. S. 20652 | 908 | | | | + | Spont. vertex | S/B | | 24 | 22 | 120 | Ample | Para iv Grav. vii |
| Mrs. S. 20836 | 1660 | | + | | | Spont. vertex | 5 | Poor | 32 | 1 1/2 | ? | Ample | Para vi Grav. vii |
| Mrs. V. 20882 | 1900 | | | + | | Spont. vertex | 4 | Poor | 31 | 5 1/2 | 36 | Ample | Para i Grav. ii |
| Mrs. L. 20930 | 1660 | | | + | | Spont. vertex | 11 | Poor | 34 | 7 | 3 | Ample | Para 0 Grav. i |
| Mrs. F.-B 21122 | 570 | | + | + | | Spont. O.P. | 4 | Poor | 28 | 3 1/2 | 0 | Not estimated | Para 0 Grav. ii |
| Mrs. F.-A 21123 | 690 | | + | | + | Spont. vertex | S/B | | 28 | 3 | 0 | Not estimated | Para 0 Grav. ii |
| Mrs. B. 21428 | 1690 | | | + | | Spont. vertex | 9 | Good | 28 | 4 | 18 | Not estimated | Para i Grav. ii |
| Mrs. H. 21848 | 700 | | | + | | Spont. vertex | 12 | Poor | 24 | 0 | 24 | Not estimated | Para 0 Grav. i |
| Mrs. F. 21899 | 795 | | | + | | Assisted breech | 1 1/2 | Poor | 25 | 8 | 1/2 | Not estimated | Para i Grav. ii |
| Mrs. L. 21966 | 600 | | | | + | Spont. vertex | S/B | | 25 | 36 | 0 | Not estimated | Para iv Grav. v |
| Mrs. C.-A 22076 | 390 | | | + | | Spont. vertex | S/B | | 23 | 8 | 1 | Not estimated | Para 0 Grav. iii |
| Mrs. C.-B 22077 | 360 | | | + | | Spont. vertex | S/B | | 23 | 8 | 1 | Not estimated | Para 0 Grav. iii |

TABLE V. HEAD INJURIES IN BABIES UNDER THIRTY-FIVE WEEKS' GESTATION, 38 CASES, JULY 1, 1933 TO FEB. 28, 1936

| NAME ACCESSION NUMBER | WEIGHT | DURAL LACERATION | SUBDURAL HEMORRHAGE | SUBARACHNOID HEMORRHAGE | CEREBRAL AND VENTRICULAR HEMORRHAGE | METHOD OF DELIVERY | AGE HOURS | APPEARANCE AT BIRTH | GESTATION WEEKS | DURATION OF LABOR HOURS | DRY HOURS | PELVIS | PARITY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mrs. Mc. 19378 | 2260 | + | + | + | | Spont. vertex | 16 | Poor | 32 | 6 | 26 hr. | Not estimated | Para 0 Grav. i |
| Mrs. B. 19382 | 1520 | + | + | + | | Spont. vertex | 21 | Poor | 32 | 12 | 72 hr. | Clinically ample | Para ii Grav. iii |
| Mrs. C. 19431 | 1900 | | | | + | Spont. vertex | 14 | Poor | 28 | 6 | 5 min. | Ample | Para 0 Grav. i |
| Mrs. S. 19460 | 1910 | + | + | | | Spont. vertex | 9 | Cyanosis | 33 | 17½ | 24½ hr. | Ample | Para 0 Grav. i |
| Mrs. N. 19497 | 520 | | | + | | Spont. vertex | ½ | Poor | 25 | 14 | 21 hr. | Ample | Para 0 Grav. i |
| Mrs. D. 19524 | 1845 | | | + | | Spont. vertex | 4 | Poor | 31 | 23 | ¼ hr. | Ample | Para 0 Grav. i |
| Mrs. G. 19672 | 730 | + | + | | | Assisted breech | S/B | | 24 | 4¼ | 60 hr. | Not estimated | Para 0 Grav. i |
| Mrs. G. 19677 | 2215 | + | + | | | Spont. vertex | 11 | Cyanotic | 33 | 28½ | 28½ hr. | Not estimated | Para ii Grav. iii |
| Mrs. R.-A 19736 | 1035 | | | | + | Spont. vertex | 8 | Poor | 25 | 52½ | 0 | Ample | Para i Grav. ii |
| Mrs. R.-B 19742 | 935 | | | | + | Spont. vertex | 4 | Poor | 25 | 54½ | 0 | Ample | Para i Grav. ii |
| Mrs. G. 19762 | 1185 | | | + | | Spont. vertex | 1 | Poor | 28 | 1 | ½ hr. | Not estimated | Para 0 Grav. i |

TABLE VI. HEAD INJURIES IN BABIES UNDER 35 WEEKS' GESTATION, 38 CASES, JULY 1, 1933 TO FEB. 28, 1936

| NAME ACCESSION NUMBER | WEIGHT | DURAL LACERATION | SUBDURAL HEMORRHAGE | SUBARACHNOID HEMORRHAGE | CEREBRAL AND VENTRICULAR HEMORRHAGE | METHOD OF DELIVERY | AGE | APPEARANCE AT BIRTH | GESTATION WEEKS | DURATION OF LABOR HOURS | DRY HOURS | PELVIS | PARITY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mrs. C. 22087 | 960 | | | | + | Spont. vertex | S/B | | 26 | | | | |
| Mrs. L. 21360 | 1700 | + | + | + | | Spont. vertex | 8 days | Fair | 30 | 3 | 1 | Ample | Para 0 Grav. i |
| Mrs. S. 21530 | 1900 | | | + | | Spont. vertex | 8 days | Fair | 28 | 15 | 18 | Not estimated | Para 0 Grav. i |
| Mrs. A. 22358 | 1200 | + | + | | | Assisted breech | 3 hr. | Poor | 30 | 5½ | 0 | Ample | Para ii Grav. iii |
| Mrs. M. 22617 | 1700 | + | + | + | | Forceps low No episiotomy | 4 hr. | Good | 30 | 15½ | 0 | Ample | Para 0 Grav. i |
| Mrs. Z. 22633 | 1550 | | + | + | + | Spont. vertex | 6 hr. | Poor | 29 | 62 | 61 | Ample | Para 0 Grav. i |
| Mrs. S. 22920 | 850 | | | + | + | Spont. vertex | 9 days | Fair | 31 | 3 | | Not estimated | Para i Grav. vi |
| Mrs. M. 22927 | 1250 | | | | + | Spont. vertex | 3 hr. | Poor | 28 | 10 | 28 | Ample | Para i Grav. iii |
| Mrs. D. 22946 | 800 | | + | | + | Spont. vertex | 4 hr. | Fair | 25 | 22½ | 48 | Not estimated | Para ii Grav. iv |

these vessels burst. Distention reflected backward along the dural sinuses through the great cerebral vein would account for the rupture of the weak tributary vessels beneath the floor of the lateral ventricles. A common result of the same forces in the term infant is the caput succedaneum which on section always shows a hemorrhagic edema. This explanation is very similar to that offered by Abels[9] in 1913.

In order to determine more clearly the effect of labor and the method of delivery in the premature infant, 249 consecutive cases occurring between June 1, 1934 and June 1, 1936 were studied. Tables VII and VIII show the relationship of prolonged labor, with and without ruptured membranes, to the incidence of intracranial injury in those stillbirths and infants who came to autopsy. Among the primiparas there is a very definite trend to an increased incidence of injury in prolonged labor and a less definite one in the cases of dry labor. On the other hand among the multiparas, the figures do not permit any conclusion to be drawn.

This series of premature infants was delivered by a number of different methods. The group was broken up according to the various techniques employed. Spontaneous delivery of the premature infant occurred in 153 cases. Table IX shows the result in 57 cases occurring in primiparas. Allowing for certain corrections, eliminating macerated fetuses, anencephalics, and those cases not coming to autopsy, it was

TABLE VII. RELATION OF DURATION OF LABOR AND OF DRY LABOR TO OCCURRENCE OF INTRACRANIAL SURGERY IN PREMATURES BASED ON AUTOPSIES

PRIMIPARAS

| DURATION OF LABOR; HOURS | LABOR | | | DRY LABOR | | |
|---|---|---|---|---|---|---|
| | NO INJURY | INJURY | % INJURED | NO INJURY | INJURY | % INJURED |
| 5 | 10 | 2 | 16.1 | 14 | 9 | 39.1 |
| 10 | 6 | 2 | 25.0 | 2 | 3 | 60.0 |
| 15 | 2 | 2 | 50.0 | 1 | 0 | 0 |
| 20 | 1 | 4 | 80.0 | 1 | 3 | 75.0 |
| 30 | 1 | 3 | 75.0 | 0 | 0 | 0 |
| 40 | 3 | 1 | 25.0 | 2 | 0 | 0 |

TABLE VIII. RELATION OF DURATION OF LABOR AND OF DRY LABOR TO OCCURRENCE OF INTRACRANIAL SURGERY IN PREMATURES BASED ON AUTOPSIES

MULTIPARAS

| DURATION OF LABOR; HOURS | LABOR | | | DRY LABOR | | |
|---|---|---|---|---|---|---|
| | NO INJURY | INJURY | % INJURED | NO INJURY | INJURY | % INJURED |
| 5 | 10 | 9 | 47.3 | 15 | 8 | 34.7 |
| 10 | 3 | 3 | 50.0 | 0 | 0 | 0 |
| 15 | 3 | 0 | 0 | 1 | 1 | 50.0 |
| 20 | 2 | 1 | 33.3 | 0 | 0 | 0 |
| 30 | 1 | 0 | 0 | 0 | 0 | 0 |
| 40 | 0 | 0 | 0 | 1 | 1 | 50.0 |

found that 62.5 per cent of the autopsied cases showed intracranial injury and that the incidence of this lesion in the entire group was 34.8 per cent. Table X shows the results in 96 cases occurring in multiparas. Again allowing for the same corrections, it was found that 44 per cent of the autopsied cases showed intracranial lesions, while the incidence of these injuries for the group was 14.4 per cent. The marked difference in incidence of intracranial injury following primiparous labors as compared to multiparous labors suggests strongly that many of these injuries may occur during the second stage of labor and that they are due to the greater resistance offered by the perineal structures in the former type of patient.

TABLE IX. PRIMIPARAS

| | | |
|---|---|---|
| Spontaneous vertex deliveries without episiotomy | 57 | |
| Total stillbirths and neonatal deaths | 38 | (66%) |
| Macerated fetus; no autopsy; anencephalic | 14 | |
| Total autopsied prematures considered | 24 | |
| Intracranial injuries found at autopsy | 15 | (62.5%) |
| Total of prematures considered (Excluding macerated fetuses, anencephalics and cases not autopsied) | 43 | |
| Percentage of intracranial injury in prematures delivering spontaneously without episiotomy | 34.8% | |

TABLE X. MULTIPARAS

| | | |
|---|---|---|
| Vertex—spontaneous without episiotomy | 96 | |
| Total stillbirth and neonatal deaths | 45 | (47%) |
| Macerated fetus; no autopsy; anencephalic | 20 | |
| Total autopsied prematures considered | 25 | |
| Intracranial injury found at autopsy | 11 | (44%) |
| Total of prematures considered (Excluding macerated fetuses, anencephalics; and cases not autopsied) | 76 | |
| Percentage of intracranial injury in prematures delivering spontaneously without episiotomy | 14.4% | |

A second group of vertex presentations was found in which the second stage had been shortened by various procedures. Table XI shows the results in spontaneous delivery in 8 primiparas following episiotomy. Three stillbirths and neonatal deaths occurred in this group. No intracranial injuries were found in those prematures who came to autopsy. No such group was found among the multiparas. Table XII shows the results of forceps delivery with episiotomy in 31 primiparas. Four stillbirths and neonatal deaths occurred. Again no intracranial injuries were discovered in those prematures who came to autopsy. No instance was found in which this procedure was used on a multiparous patient. Tables XIII and XIV show the results in 8 cases delivered by low forceps without episiotomy. Three were in primiparas. Only 1 infant survived, and of the 2 lost, 1 came to autopsy and showed

an intracranial injury. Five were in multiparas and no traumatic lesions were found in 3 infants who came to autopsy. Of the remaining patients 30 delivered as breech presentations, and 6 by cesarean section. Time does not permit the presentation of these tables. However, it was found, particularly in the primiparas, that intracranial injury was less likely to occur when an episiotomy was performed before delivering the aftercoming head. These figures suggest that, while injury may occur during the first stage, more commonly it is produced in the second stage of labor, and that it occurs more commonly when the mother is a primigravida. If this is the case, the incidence of these lesions can be markedly reduced by certain procedures. The problem of the care of the premature infant is not only confined to the neonatal period but also concerns the intrapartum period. It is felt that the obstetrician can, with proper care, diminish the number of handicapped infants who are passed over into the hands of the pediatrician.

In closing it seems worth considering how these injuries may be minimized. Prevention of these injuries involves two considerations.

TABLE XI. PRIMIPARAS

| | |
|---|---|
| Spontaneous vertex delivery with episiotomy | 8 |
| Total stillbirths and neonatal deaths | 3 |
| Correction | 0 |
| Intracranial injury found at autopsy | 0 |
| Percentage | 0% |

TABLE XII. PRIMIPARAS

| | |
|---|---|
| Forceps delivery with episiotomy | 31 |
| Total stillbirths and neonatal deaths | 4 |
| Correction | 0 |
| Intracranial injury found at autopsy | 0% |

TABLE XIII. PRIMIPARAS

| | |
|---|---|
| Forceps delivery without episiotomy | 3 |
| Total stillbirths and neonatal deaths | 2 |
| Intracranial injury found at autopsy | 1 |
| Correction—no autopsy | 1 |
| Percentage of intracranial injury found at autopsy | 100% |
| Percentage intracranial injuries in prematures delivered with low forceps without episiotomy | 50% |

TABLE XIV. MULTIPARAS

| | |
|---|---|
| Vertex—forceps delivery without episiotomy | 5 |
| Total stillbirths and neonatal deaths | 3 |
| Correction—not autopsied | 1 |
| Total autopsied prematures considered | 2 |
| Intracranial injury found at autopsy | 0 |

The first, the avoidance of unnecessary induction of labor. The second, the elimination of excessive compression in the second stage. Let us consider the first stage of labor.

Many cases of premature labor are initiated by rupture of the membranes. Because of the unwarranted fear of amniotic sac infection, it is a common practice to induce labor in such cases and to perform rectal or vaginal examinations at frequent intervals to determine the character of the cervix. If such a patient has a soft, retracted and partially dilated cervix, she will go into labor inevitably within twenty-four hours. If, on the other hand, the cervix is closed, firm, and unretracted, it is possible that pregnancy may proceed for several days or even weeks before labor begins. Induction in this type of patient, on the other hand, often produces a protracted first stage. An amniotic sac infection seldom occurs in a patient who is not in labor unless organisms are carried into the cervix or lower uterine segment by the examining finger, either vaginally or rectally. The protection of the sac probably depends on the constant formation and leakage downward of amniotic fluid and the presence of a closed unretracted cervix. When such a patient goes into spontaneous labor, it is frequently found that the cervix is adequately prepared and the duration of the process is usually short. This method of dealing with patients who have premature rupture of the membranes has been a routine practice at Bellevue Hospital for the past three years. Only one instance of amniotic sac infection has been observed among these patients treated by simple bed rest. This occurred in a patient who was examined vaginally under the mistaken impression that she had begun labor. It is believed that this policy will often allow the patient to continue pregnancy to a point closer to term and that it will terminate in a shorter, easier labor. Both of these results will reduce the incidence of intracranial injury.

The induction of premature labor in the presence of resistant soft parts in order to bring a small fetus through a borderline pelvis is to be condemned. An induced labor is frequently prolonged and the premature infant often sustains injuries during the process.

Of even greater importance is the conduct of the second stage of labor. During this period it is possible to definitely shorten the process and to reduce the forces to which the premature is exposed, particularly in the primiparous patient. This can readily be done by anesthetizing the mother and delivering the fetus by low forceps and episiotomy. Voluntary efforts on the part of the mother in the presence of resistant soft parts are to be discouraged. A cephalic application of forceps is of even greater importance than in the term infant.

The Simpson type of forceps is best adapted to this type of delivery owing to its wide cephalic curve. This procedure is of particular value if the perineal structures offer marked resistance. It is believed that the routine use of this maneuver will result in a marked reduction of intracranial injuries in the premature infant.

Finally, efforts to restrain the premature fetal head by manual pressure in order to avoid a precipitate delivery or because an attending physician is not present, should be avoided. In the premature such efforts may result in intracranial injury.

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768 Park Avenue

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## INTERNAL PELVIMETRY AS A BASIS FOR THE MORPHOLOGIC CLASSIFICATION OF PELVES

Samuel Hanson, A.M., M.D., F.A.C.S., Stockton, Calif.
*(From the San Joaquin General Hospital)*

THE work of Caldwell and Moloy[1] shows that much useful information can be gained by studying the morphology of the pelvis as a whole in a purely descriptive qualitative way. This approach to the study of the subject, however, does not lessen the importance of quantitative methods; on the contrary, it gives promise of increasing the practical value of pelvic measurements by providing a more scientific basis for pelvimetry. Conversely, methods of precision simplify and increase the usefulness of morphologic classifications.

The aim of the present study is to assemble the most practical methods available for the measurement of the important classical diameters of the pelvis, and to supplement these with new methods for the measurement of the dimensions which the recent contributions of Caldwell and his associates have brought to light. The dimensions selected for measurement are those which are of greatest significance in the morphologic classification of Thoms,[2] and of Caldwell and Moloy.[1] A special effort is made to facilitate the recognition of male or android characters.

## THE PELVIC OUTLET

The narrow subpubic angle has long been recognized as the most important character of the contracted pelvic outlet. Its width can be computed from the length of the anterior sagittal and transverse diameters of the outlet. There are, however, two sources of error in this method: First, the intertuberous diameter cannot be measured accurately, due to the variable thickness of the fat pad which covers the

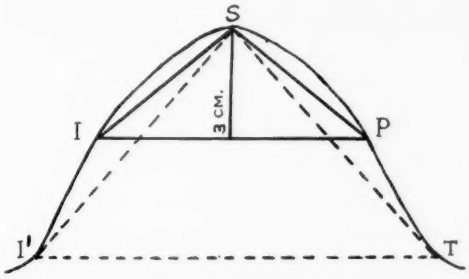


Fig. 1.—The pubic arch: *I'.T.*, Intertuberous diameter; *I.P.*, interpubic diameter: *I.S.P.*, subpubic angle.

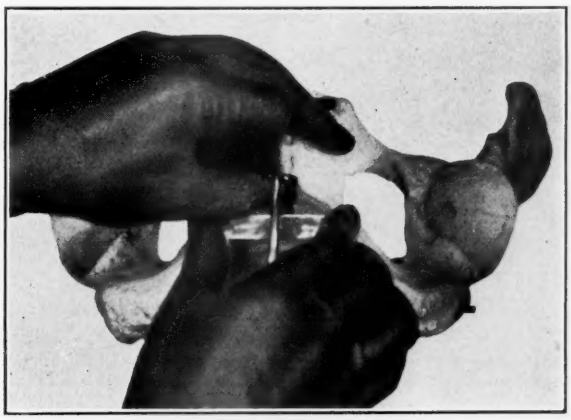

Fig. 2.—The measurement of the interpubic diameter. A gauge is fitted between the pubic rami at a distance of 3.0 cm. below the apex of the pubic arch. This distance is determined with the rectal blade of the internal pelvimeter.

tuberosities of the ischia. Second, the lateral curvature of the ischiopubic rami is overlooked if the subpubic angle is estimated with the ischial tuberosities forming the base of the triangle (Fig. 1). Both of these sources of error can be minimized by selecting a point nearer to the pubic arch to form the base of the triangle from which the subpubic angle is to be computed. A point 3 cm. below the apex of the pubic arch was arbitrarily selected for this purpose. The transverse dimension of the outlet at this level will be designated as the interpubic diameter (Fig. 1). The width of the interpubic diameter can be readily deter-

mined by fitting a gauge between the pubic rami at a perpendicular distance of 3.0 cm. below the inferior border of the symphysis pubis (Fig. 2). Five-tenths centimeter is added to the reading obtained to compensate for the thickness of the soft tissues covering the pubic rami.

The width of the subpubic angle in the last 100 consecutive cases, as determined in this manner, was found to vary between 95 degrees and 132 degrees (average 107 degrees). A subpubic angle of 100 degrees or less may be regarded as an android character. There were 8 cases in the present series in which the subpubic angle was contracted to this degree.

### THE DIMENSIONS OF THE NARROW PELVIC PLANE

The plane of least dimensions, or narrow pelvic plane has been defined as the level of the pelvis which is bounded anteriorly by the lower border of the symphysis pubis, laterally by the ischial spines, and posteriorly by the tip of the sacrum. These three points are, however, not truly in the same plane, since the tip of the sacrum is approximately 2 cm. below the level of a line joining the apex of the pubic arch with the bispinous diameter. Furthermore, measurements taken from the tip of the sacrum are at too low a level to serve as an index of the sagittal dimensions of the mid, and upper posterior pelvis.[1] In the present study the junction of the fourth and fifth sacral segments is therefore selected to represent the posterior limit of the narrow pelvic plane. By raising the posterior boundary even by as little as one sacral segment a more representative picture is obtained of the width of the sacrosciatic notch, and of posterior pelvic capacity. This is of great importance in the recognition of the android pelvis.[1]

Other significant essentially android characters, according to my own observations, are the contracted bispinous and interischial diameters, and the narrow retropubic angle.

Methods for the measurement of these important dimensions of the narrow pelvic plane are presented in the sections to follow.

### THE TRANSVERSE DIAMETERS OF THE NARROW PELVIC PLANE

My interest has long been focused on the bispinous and interischial diameters. In previous communications[3, 4] I submitted methods for the measurement of these diameters. For the sake of completeness a description of these methods is again presented in abbreviated form. The procedure for the measurement of the bispinous diameter is briefly as follows:

The blades of the pelvimeter (Fig. 3) are separated. "The tip of the middle finger of the right hand is inserted into the ring of the vaginal blade (*V*). With the blade in place the index and middle fingers are

introduced into the vagina. The tip of the index finger of the left hand is similarly placed within the ring of the rectal blade (*R*), and is introduced into the rectum. The two blades are now locked and the spinous processes are identified. The rings are then steadied against the tips of the spinous processes, and a reading is made on the scale."[3] The interischial diameter is measured similarly, with the exception that the rings are carried anteriorly to the bases of the ischial spines when the reading is taken.

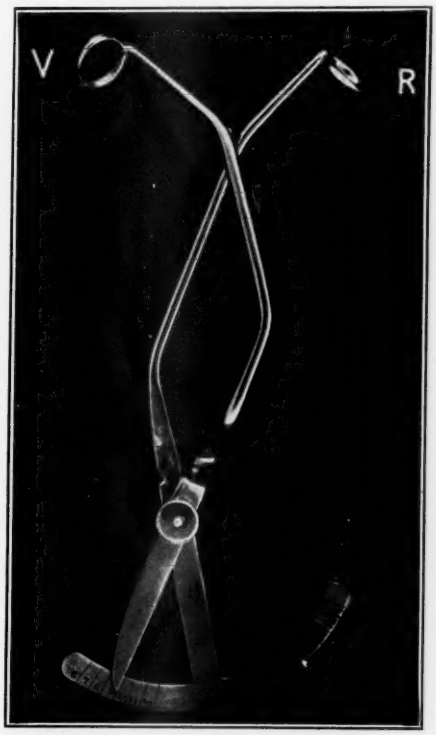


**Fig. 3.—The internal pelvimeter: *R.*, rectal blade; *V.*, vaginal blade.**

Statistical data on the bispinous and interischial diameters were presented in a previous report.[4] Values for these diameters of 9.5 cm. and 10.0 cm., respectively, may be regarded as the lower limits of normal.

## SAGITTAL DIAMETERS OF THE NARROW PELVIC PLANE

Early in the course of studies on the transverse diameters of the narrow pelvic plane my attention was drawn to the sagittal diameters. In 1932 I took measurements of these diameters in selected cases, but failed to appreciate their full significance. The recent work of Caldwell and Moloy stimulated my interest in the subject, and prompted me to devise simple and accurate methods for the measurement of the diameters under consideration.

The length of the anterior sagittal diameter is derived from values obtained by direct measurement of the bispinous and spinopubic diameters (Fig. 4). The length of the posterior sagittal diameter is determined by subtracting the value of the anterior sagittal from that of the sacropubic diameter.

For the measurement of the spinopubic diameter the vaginal blade is attached to the rectal blade in the reverse position (Fig. 5). The tip of the left index finger is passed into the ring of the rectal blade, and the blade resting on the dorsum of the finger is introduced into the rectum. The left ischial spine is identified and the ring is steadied against its tip while the lower border of the ring of the vaginal blade, held between the thumb and index finger of the other hand, is brought

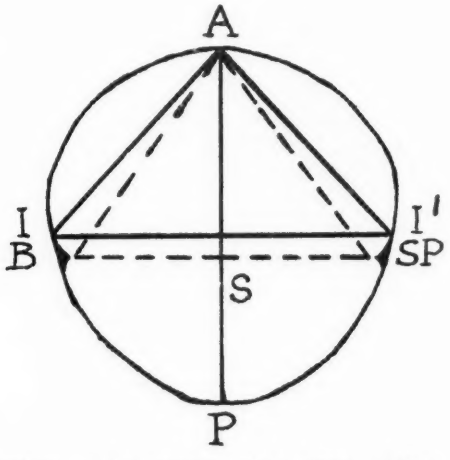


Fig. 4.—The diameters of the narrow pelvic plane: *B.SP.*, bispinous diameter; *A.SP.*, spinopubic diameter; *A.S.*, anterior sagittal diameter; *P.S.*, posterior sagittal diameter; *I.I'*, interischial diameter; *I.A.I'*, retropubic angle.

up against the inferior border of the symphysis pubis. A reading is made on the scale while the rings are held in this position.

The sacropubic diameter is measured in a similar manner, as previously described.[5] The reading is taken while the ring of the rectal blade is held against the sacrum at the junction of the fourth and fifth segments, while the ring of the vaginal blade is brought up against the inferior border of the symphysis pubis. The junction of the fourth and fifth sacral segments is located by advancing the rectal ring internally along the sacrum until the distal interphalangeal joint of the finger carrying the ring comes to rest on the tip of the sacrum. The ring is thus placed at a distance above the tip of the sacrum equal in length to the length of the terminal phalanx of the index finger (about 2 cm.), which is approximately the junction of the fourth and fifth sacral segments. This localization is sufficiently accurate for all practical purposes.

The length of the sagittal diameters of the narrow pelvic plane was determined in the manner described in a series of 100 consecutive cases. The spinopubic diameter measured from 7.3 cm. to 9.4 cm. (average 8.30 cm.). The length of the anterior sagittal diameter was found to vary between 4.7 cm., and 7.4 cm. (average 6.48 cm.), and that of the posterior sagittal between 3.5 cm. and 8.0 cm. (average 5.59 cm.). In 19 cases the posterior sagittal diameter was longer than the anterior sagittal. A posterior sagittal diameter of 4.5 cm. or less may be regarded as an android character. There were 8 such cases in the present series.

Fig. 5.—Measurement of the sacropubic diameter. Vaginal blade reversed. Ring of rectal blade placed at junction of fourth and fifth sacral segments, while ring of vaginal blade is brought up against the inferior border of the symphysis pubis.

## THE DIMENSIONS OF THE PELVIC INLET

Thoms' x-ray method[6] was found to be satisfactory for the measurement of the dimensions of the inlet. The following minor modification was made to simplify the procedure:

An ordinary level is substituted for the plump-bob in estimating the height of the upper border of the pubis from the x-ray table. In so doing the interference of a protruding abdomen is avoided. The grid is adjusted to the proper height from points representing the upper

inner border of the pubis, and the space between the fourth and fifth lumbar vertebrae, as in Thoms' original method.

The important android characters of the pelvic inlet, according to Caldwell and Moloy, are the short posterior sagittal diameter, the relatively long straight anterior puboiliac portions, and the narrow retropubic angle. These characters can be readily determined quantitatively on a Thoms film (Fig. 6). A posterior sagittal diameter of 3.5 cm. or less may usually be regarded as distinctly android.

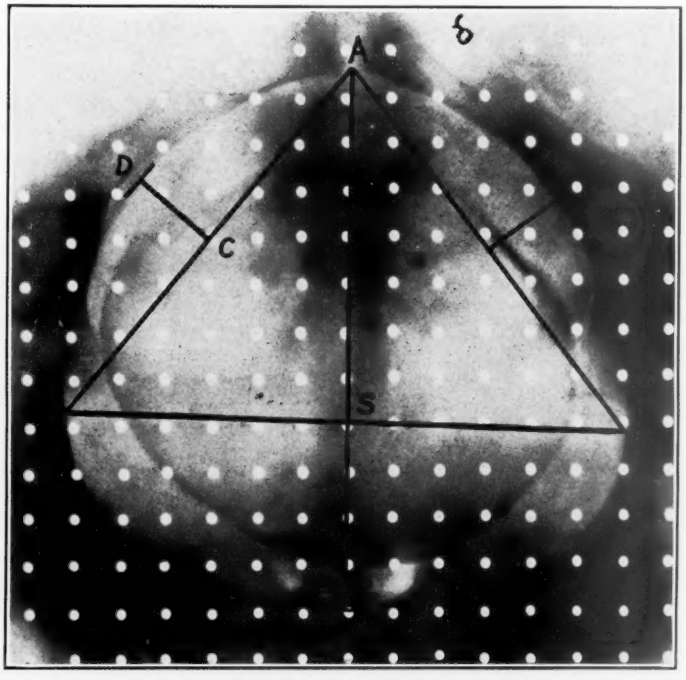


Fig. 6.—The dimensions of the pelvic inlet: *T.R.*, transverse diameter; *P.S.*, posterior sagittal diameter; *T.A.R.*, retropubic angle; *D.C.*, degree of curvature of anterior puboiliac portion.

## THE MORPHOLOGIC CLASSIFICATION OF PELVES

The recent contributions of Caldwell and his associates mark a distinct advance in our knowledge of the android pelvis. The android characters to which these observers call attention are clear-cut, and unmistakable. This, however, cannot be said of the other three types in their classification. The identification of the gynecoid, anthropoid and platypelloid types can be made with certainty only from a study of the contour of the pelvic inlet. The differentiation of these three types at lower levels of the pelvis is confusing and tends to detract from the significance of the android characters which are often present in all these forms, and which deserve a place of greatest prominence in any classification. For practical purposes it may therefore be advantageous

to give a subordinate place to the anthropoid and platypelloid forms, and to regard these merely as varieties of the gynecoid type.

The following is a simple morphologic classification of pelves based on the classifications of Thoms,[2] and of Caldwell and Moloy.[1]

1. *Gynecic (JIN-E'SIK) Pelves:*
   - (a) Mesatipellic (round)
   - (b) Dolichopellic (oval); sagittal diameter of inlet longer than transverse diameter.
   - (c) Brachypellic (oval); sagittal diameter of inlet shorter than transverse diameter.
   - (d) Platypellic (flat); sagittal diameter of inlet excessively shorter than transverse diameter.
   - (e) Asymmetric
2. *Android Pelves.*

The term "gynecic" (pertaining to women) is preferable to the term "gynecoid" which literally refers to the male pelvis with female characters.

The terms mesatipellic, dolichopellic, brachypellic, and platypellic are used only with reference to the pelvic inlet, in accordance with Thoms' definitions.[2] It is, however, assumed, unless otherwise stated, that the lower pelvis in these forms possesses essentially normal female characters.

The various gynecic types may have android abnormalities at the inlet, midpelvis or outlet; and conversely, the android pelvis may have gynecic characters at various levels. The mixed forms may be classed as android-gynecic or gynecic-android, depending on whether the male characters predominate at the pelvic inlet or at lower levels of the pelvis, respectively.

A subdivision of the above pelvic types into large, medium and small may be made, but such a subgrouping should be supplemented with quantitative data for all the important dimensions of the pelvis.

A careful morphologic classification of pelves is desirable in most cases. The expense of routine x-ray pelvimetry is, however, still considered prohibitive in most clinics. For the present, x-ray measurements must, therefore, be limited to selected cases. Internal instrumental pelvimetry may serve as a guide to the selection of cases for x-ray study. For practical purposes, a pelvis may usually be regarded as normal or gynecic, on the basis of clinical findings alone, when the promontory of the sacrum cannot be reached (C.D. of 12+), and when the subpubic angle, and the posterior sagittal and transverse diameters of the narrow pelvic plane are within normal limits. X-ray pelvimetry, however, becomes indispensable when a contraction is found in any one of these important dimensions. Under such circumstances all the diameters of the pelvic inlet must be accurately determined, and an absolutely correct diagnosis of the pelvic type must be made. The same applies to all forms

of asymmetric pelves, and to all cases where disproportion may be suspected, especially in primiparas at term with no engagement of the presenting part, and in multiparas with a history of previous complicated labors.

SUMMARY

Instrumental procedures of internal pelvimetry are supplemented by Thoms' x-ray method to provide quantitative data for the morphologic classification of pelves. Special emphasis is placed on android characters.

The width of the subpubic angle is computed from modified measurements of the anterior sagittal and transverse diameters of the outlet.

The bispinous and interischial diameters, and the anterior and posterior sagittal diameters of the narrow pelvic plane, are measured by means of an internal pelvimeter previously described which was especially designed for this purpose.

The diameters of the pelvic inlet are determined on a Thoms film. The dimensions measured are the transverse and the anterior and posterior sagittal diameters. The retropubic angle and the degree of curvature of the anterior puboiliac portions are also determined.

A morphologic classification of pelves is presented which is based on the classification of Thoms, and of Caldwell and Moloy.

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1009 Medico-Dental Building.

ADDENDUM

*The Posterior Sagittal Diameter of the Midplane.*—As stated above, the posterior sagittal diameter at higher levels of the pelvis is an accurate index of the width of the sacrosciatic notch, and of posterior pelvic capacity. The determination of the length of the posterior sagittal diameter of the midplane is therefore desirable. This can readily be accomplished as follows:

The patient is placed on the side, and a point is marked on the sacrum equidistant from the lumbosacral interspace and the tip of the sacrum. The patient is then placed in the lithotomy position with the buttocks well over the end of the table. With an ordinary external pelvimeter a measurement is taken from the lower border of the symphysis pubis to the point marked on the sacrum. The thickness of the sacrum and overlying soft tissues is determined with the same pelvimeter by placing the tip of one arm of the instrument against the sacrum internally through

the rectum, while the tip of the other arm is brought up externally against the sacrum at the point marked.

The length of the posterior sagittal diameter of the midplane is now determined by subtracting from the first measurement the reading obtained for the thickness of the sacrum, and the value previously obtained for the length of the anterior sagittal diameter of the narrow pelvic plane.

A posterior sagittal diameter of the midplane of 5.5 cm. or less may usually be regarded as an android character.

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## THE COMPARATIVE EFFECTS OF PREGNANCY AND PHRENIC NERVE INTERRUPTION ON THE DIAPHRAGM AND THEIR RELATION TO PULMONARY TUBERCULOSIS

A. PARK MCGINTY, M.D., ATLANTA, GA.

*(From the Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan)*

AS LONG as women have tuberculosis, the medical profession will be faced with the problem of tuberculosis and pregnancy. At the present time there is no unanimity of opinion as to how a pregnant woman with tuberculosis should be treated. Notwithstanding the multitudinous opinions on this subject, there are insufficient scientific data upon which to base a sound conclusion. In this paper we do not wish to discuss the problem as a whole, but wish merely to direct attention to one phase of it. *This study is concerned with the hypothesis that the pregnant uterus has an effect upon the diaphragm similar to that produced by section of the phrenic nerve, namely elevation and paralysis of the diaphragm.*

In attempting to trace the development of the present ideas concerning the action of the diaphragm in pregnancy, we searched 120 obstetric textbooks of separate titles supplemented by 50 later editions.

The first reference to the diaphragm was found in the 1831 translation by Meigs of Velpeau's work.[1] It states: "The diaphragm itself being pushed upward into the thorax, whose base it enlarges, while its vertical diameter is lessened, is in some degree hindered from executing its contractile movement." In 1866 Dohrn found that in most cases the base of the thorax during pregnancy has a greater transverse but smaller anteroposterior diameter, thus partially compensating for the decreased vertical diameter. In succeeding works, these two ideas have been continued in part or in whole. By 1907[2] the addition of a third idea had appeared, namely, that during pregnancy the breathing is more thoracic than abdominal in type. The latest works available[3-6] continue the same ideas. For instance, DeLee[7] states: "The respiration is more costal than abdominal because of the restricted excursion of the diaphragm; yet the lung capacity is increased, breathing deeper and more frequently—cause, acidosis?"

The only book found that differs from the above mentioned ideas is the 1890 English translation of Winckel[8] of the University of Munich. In this book it is stated: "The lungs are dragged apart, but the vital capacity is not interfered with, for Kuckenmeister, Fabins, Wintrich, and more recently Vejas (in my clinic) have not been able to find any such change, even in the last month. . . . Gerhardt, in forty-two cases, found the *diaphragm* higher than usual in one case only; in thirty-six its position was normal."

Since artificial pneumothorax and phrenic nerve interruption have become popular in the treatment of pulmonary tuberculosis, one of the arguments frequently given for the conservation of pregnancy in a tuberculous patient is that the gravid uterus elevates the diaphragm and acts as a splint, thus giving the effect of a phrenic palsy or pneumothorax. This hypothesis has been used as an argument that pregnancy would be as beneficial to the pulmonary lesions as a bilateral section of the phrenic nerves. It has also been used in the suggestion that after delivery of a tuberculous woman, the phrenic nerves should be sectioned to maintain the paralysis of the diaphragm that was supposed to have existed during the latter months of pregnancy.

The basis of this argument has been expressed by Professor Sergent[9] of France as follows: "The apparent improvement that is observed during the latter months of pregnancy is due to the upward displacement of the diaphragm, thus creating a sort of bilateral artificial pneumothorax." Professor Crockett[10] of St. Mungo's College, Glasgow, in 1934 stated: "When a female who is suffering from tuberculosis becomes pregnant, there is produced an increasing intra-abdominal pressure. This acts on the lung exactly like an artificial pneumothorax or a phrenic avulsion operation, which causes paralysis of the diaphragm and causes the diaphragm to rise up into the thoracic cavity."

Our observations from the fluoroscopic examination of pregnant patients did not agree with the viewpoint that the gravid uterus splints the diaphragm. Our fluoroscopic observations did agree with the observations of Heynemann[11] which were published in 1913.

Heynnemann's observations were based on a study of 42 women during the last trimester of pregnancy of whom 37 were also examined after delivery. In addition 35 nonpregnant women were examined. The examination included a thorough physical examination, fluoroscopic examination, and teleoroentgenograms or orthodiagrams. In 10 women both teleoroentgenograms and orthodiagrams were made. The teleoroentgenograms were made on quiet respiration with the subject standing, the tube being centered to the left of the spinal column at the height of the cardiac apex at a distance of 2 to 2.5 meters. Orthodiagrams were made with the subject sitting, the position of the heart and diaphragm on forced inspiration and on forced expiration being determined. From these studies Heynemann found that without exception there was an elevation of the diaphragm toward the end of pregnancy. The degree was highly variable being from 0.25 to 4 cm. The average was 2.11 cm. During quiet respiration there was no definitely recognizable difference between the pregnant and nonpregnant states. During forced respiration Heynemann found that on deepest inspiration the diaphragm cannot descend as deeply in the pregnant as in

the nonpregnant woman, but on complete expiration it rises so much higher that he "was forced to the unqualified conclusion that the excursion of the diaphragm even at the end of pregnancy is not at all or only very remarkably little impaired."

To show the difference between the effect of phrenic nerve interruption and pregnancy on the action of the diaphragm, we decided to determine the position of the diaphragm, the extent of its movement, and the direction of its movement in subjects during pregnancy and after delivery and in a subject before and after phrenic palsy. Our studies were made with the use of the teleoroentgenogram at 72 inches. The subject maintained forced inspiration while an exposure was made; she then exhaled into a spirometer and maintained the forced expiration until the second exposure had been made on the same film. Such composite negatives were made with the subject in the anteroposterior, the right posterior oblique, and the left posterior oblique projections both vertical (standing) and horizontal (lying). In the right lateral projection it was necessary to use separate films for inspiration and expiration. The tube was centered at the level of the xiphoid.

On the films thus obtained the lung borders were outlined with a wax pencil. These outlines and certain skeletal landmarks were traced on paper and from these tracings our measurements were obtained. The tracings for dolichomorphic I.K. are shown in Figs. 1 and 2. The lung borders on forced expiration are shown by a solid line; on forced inspiration the lung borders are shown by a broken line. Using the tenth thoracic vertebra as a point of comparison, and comparing the left hand outlines with the right hand ones, we see that the diaphragm level is higher antepartum than postpartum. When we compare the upper and lower outlines we see that the diaphragm is higher when the subject is lying (horizontal) than when she is standing (vertical). Comparison of the diaphragmatic excursion reveals that it is greater antepartum than postpartum and greater horizontal than vertical.

Figs. 1 and 2 were taken from the following case: I. K. (No. 267487), a healthy white female, aged fifteen years, height 163 cm., antepartum weight 57.5 kilograms, was of a dolichomorphic habitus. The antepartum studies were obtained sixteen days before the normal spontaneous delivery of a 4,260 gm. healthy infant. The postpartum studies were made on the eleventh day of the puerperium. This subject is referred to as "dolichomorphic I. K." in Tables I, II, III, and IV. Her lung outlines are portrayed in Figs. 1 and 2.

The above case of a pregnant woman is to be compared with the following case of a woman with left phrenic nerve interruption: H. W. (No. 285596), a white female, aged thirty years, height 157 cm., weight 49.5 kilograms, was of an intermediate habitus. She had minimal pulmonary tuberculosis at the left apex. Studies were obtained the day before a left temporary phrenic nerve interruption was performed and again on the thirteenth postoperative day. This subject is referred to as "H. W. (Left Phrenic)" in Tables I, II, III and IV. Her lung outlines are portrayed in Fig. 3.

In this case we assume that preoperative corresponds to postpartum, both representing the normal state, and that postoperative corresponds to antepartum. In this case the ninth thoracic vertebra is used as the point of comparison. First considering the level of the diaphragm on expiration (solid line, Fig. 3), we see that there is no marked difference between the preoperative and postoperative levels, nor is the diaphragm level affected much by a change from the vertical to the horizontal

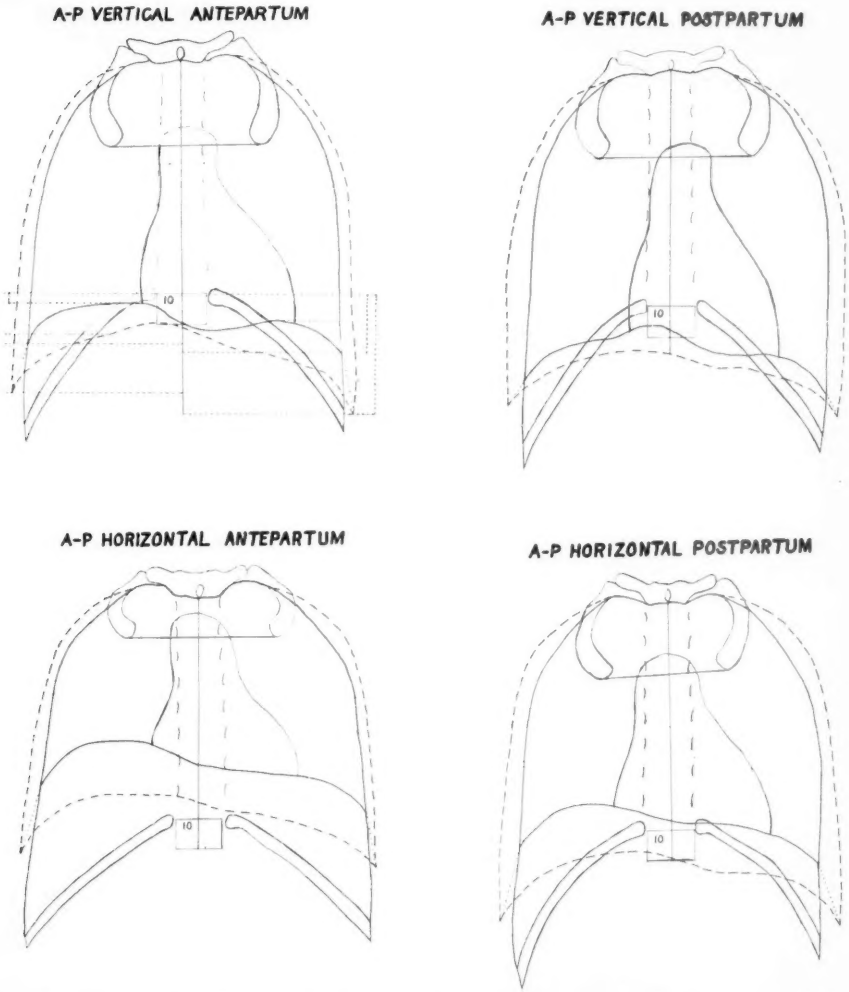


Fig. 1.—Lung outlines traced from anteroposterior teleoroentgenograms of dolichomorphic I. K. The solid line indicates their position on forced expiration; the broken line on forced inspiration. The dotted lines between the costophrenic sinuses on inspiration and expiration complete the delineation of the area of diaphragmatic excursion. In the upper left hand outline, the horizontal lines are reproduced to show the means by which the measurements were obtained for Tables III and IV.

position. This is a decided contrast to the response to pregnancy shown by dolichomorphic I. K. in Fig. 1. Next considering the right diaphragm on forced inspiration (broken line), we see that in the vertical position there is no marked difference between the preoperative and postoperative states. In the horizontal position, the diaphragmatic excursion on the right is somewhat greater postoperatively

than preoperatively. However, on the left side we find a marked difference in the presence of the left phrenic palsy. On inspiration, instead of descending as it did normally preoperatively, the left diaphragm rises. This action of the paralyzed diaphragm is known as paradoxical motion. Although it is shown to some extent in the outlines in Fig. 3, paradoxical motion can be seen to much greater advantage under the fluoroscope. It is brought out best by having the patient make a sudden inspiration in the nature of a "sniff." The paralyzed diaphragm then rises sharply

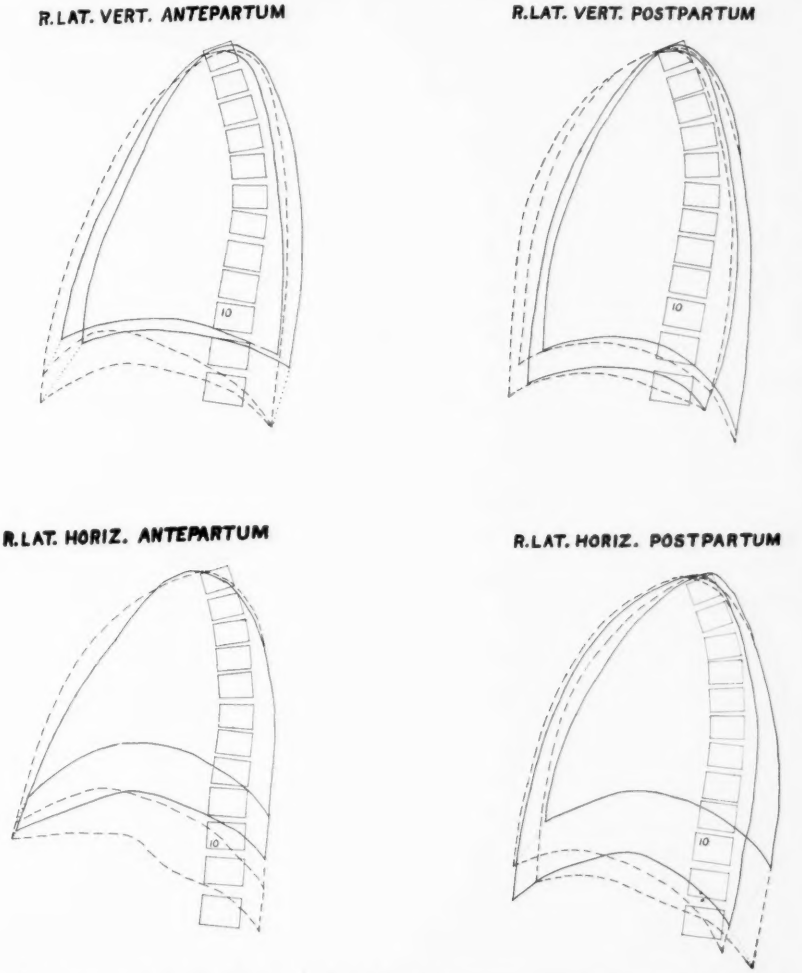


Fig. 2.—Lung outlines traced from right lateral teleoroentgenograms of dolichomorphic I. K. Solid line represents expiration; broken line inspiration.

for a fraction of a second before falling back to a less extreme position as shown in Fig. 3. In addition to the paradoxical motion of the left diaphragm postoperatively, it is seen that its excursion is much less than it was preoperatively.

In order to confirm mathematically the impressions gained from a study of Figs. 1, 2 and 3, measurements were made in following manner: In the A-P projection, a horizontal line was drawn across the upper border of the vertebra outlined, and from this line the perpendicular distance to the costophrenic sinus and to the dome

of the diaphragm on both sides on inspiration and on expiration was measured in millimeters. If there was not a definite dome, a point on the diaphragm perpendicular to the tip of the first rib was used. (See Fig. 1, left upper outline.)

With the aid of a planimeter, the area within the lung borders was determined in square centimeters. No attempt was made to subtract the contents of the mediastinum as these remain relatively constant. The area of excursion of the

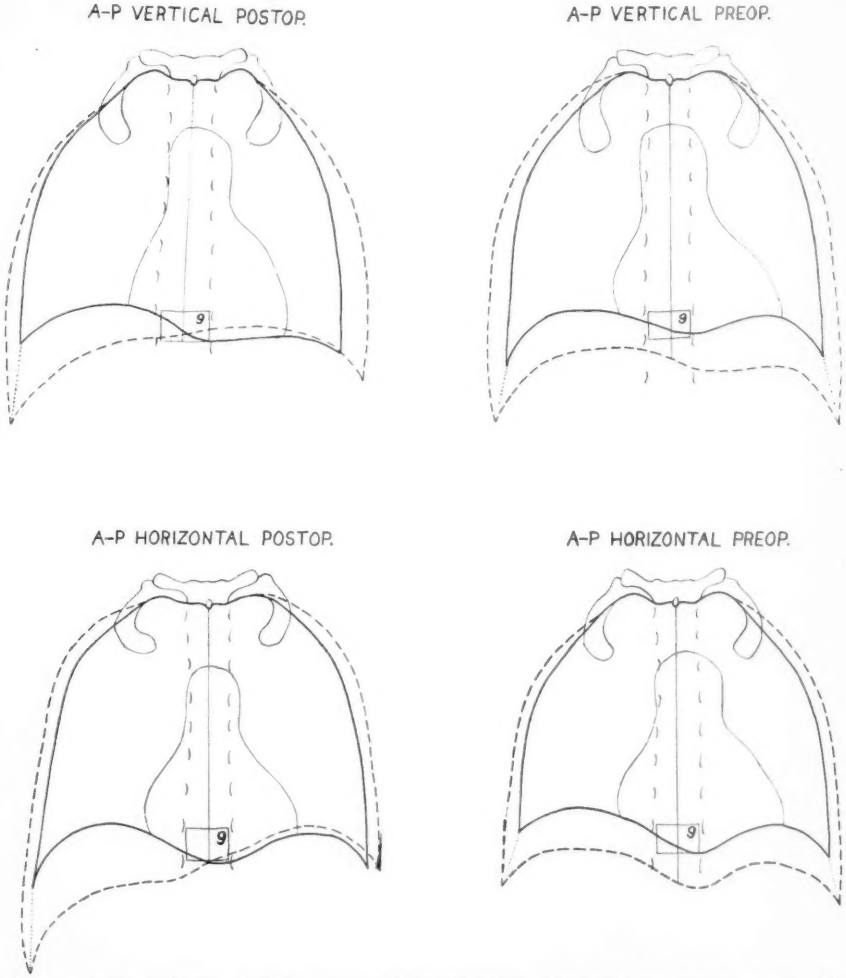


Fig. 3.—Lung outlines traced from anteroposterior teleoroentgenograms of H. W. (left phrenic). Solid line represents expiration; broken line inspiration.

lung as projected was determined by subtracting the expiratory area from the inspiratory area. The diaphragmatic excursion was determined as the area outlined by the level of the diaphragm on inspiration and on expiration supplemented by a (dotted) line drawn on either side between the costophrenic sinus in the two phases of respiration. The proportion of respiration accomplished by the excursion of the diaphragm was expressed as a percentage by dividing the area of diaphragmatic excursion by the area of the total excursion of the lung (Table I).

TABLE I*

| | SPIR. C.C. | PLANIMETER READINGS IN SQUARE CENTIMETERS | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | RIGHT | | | | | LEFT | | | | | SUM OF R. & L. | | | | |
| | | INSP. | EXP. | DIF. | DIA. | D/DIF. | INSP. | EXP. | DIF. | DIA. | D/DIF. | INSP. | EXP. | DIF. | DIA. | D/DIF. |
| *Dolichomorphic I.K.* | | | | | | | | | | | | | | | | |
| A-P. Vert. Antepartum | ---- | 228 | 178 | 50 | 27 | 54% | 267 | 214 | 53 | 27 | 51% | 495 | 392 | 103 | 54 | 52% |
| A-P. Vert. Post. | 1700 | 237 | 193 | 44 | 17 | 39% | 280 | 231 | 49 | 16 | 33% | 517 | 424 | 93 | 33 | 35% |
| A-P. Horiz. Ante. | 1790 | 183 | 124 | 59 | 47 | 80% | 213 | 150 | 63 | 43 | 68% | 396 | 274 | 122 | 90 | 74% |
| A-P. Horiz. Post. | 1790 | 230 | 159 | 71 | 45 | 63% | 243 | 176 | 67 | 37 | 55% | 473 | 335 | 138 | 82 | 59% |
| R. Lat. Vert. Ante. | ---- | 319 | 252 | 67 | 39 | 58% | 348 | 272 | 76 | 54 | 71% | 667 | 524 | 143 | 93 | 65% |
| R. Lat. Vert. Post. | 1810 | 340 | 287 | 53 | 10 | 19% | 348 | 304 | 44 | 11 | 25% | 688 | 591 | 97 | 21 | 22% |
| R. Lat. Horiz. Ante. | ---- | 271 | 178 | 93 | 73 | 78% | 334 | 249 | 85 | 69 | 81% | 605 | 427 | 178 | 142 | 80% |
| R. Lat. Horiz. Post. | ---- | 330 | 225 | 105 | 102 | 97% | 374 | 322 | 52 | 26 | 50% | 704 | 547 | 157 | 128 | 81% |
| *Brachymorphic E.C.* | | | | | | | | | | | | | | | | |
| A-P. Vert. Ante. | ---- | 226 | 180 | 46 | 32 | 70% | 240 | 194 | 46 | 33 | 72% | 466 | 374 | 92 | 65 | 71% |
| A-P. Vert. Post. | 2320 | 249 | 175 | 74 | 43 | 58% | 263 | 194 | 69 | 46 | 67% | 512 | 369 | 143 | 89 | 62% |
| A-P. Horiz. Ante. | 2250 | 191 | 129 | 62 | 43 | 69% | 197 | 141 | 56 | 33 | 59% | 388 | 270 | 118 | 76 | 64% |
| A-P. Horiz. Post. | 2360 | 248 | 149 | 98 | 62 | 63% | 231 | 154 | 77 | 47 | 61% | 479 | 303 | 175 | 109 | 62% |
| R. Lat. Vert. Ante | 2280 | 357 | 255 | 102 | 72 | 71% | 391 | 286 | 105 | 79 | 75% | 748 | 541 | 207 | 151 | 73% |
| R. Lat. Vert. Post. | 2300 | 385 | 274 | 111 | 67 | 60% | 385 | 281 | 104 | 69 | 66% | 770 | 555 | 215 | 136 | 63% |
| R. Lat. Horiz. Ante. | ---- | 325 | 220 | 105 | 77 | 73% | 367 | 259 | 108 | 78 | 72% | 692 | 479 | 213 | 155 | 72% |
| R. Lat. Horiz. Post. | ---- | 348 | 229 | 119 | 102 | 86% | 410 | 326 | 84 | 81 | 96% | 758 | 555 | 203 | 183 | 90% |
| *H.W. (Left Phrenic)* | | | | | | | | | | | | | | | | |
| A-P. Vert. Postop. | 1900 | 209 | 161 | 48 | 35 | 73% | 193 | 168 | 25 | –5 | –20% | 402 | 329 | 73 | 30 | 41% |
| A-P. Vert. Preop. | 1800 | 222 | 167 | 55 | 33 | 60% | 217 | 159 | 58 | 35 | 60% | 439 | 326 | 113 | 68 | 60% |
| A-P. Horiz. Postop. | 1250 | 235 | 164 | 71 | 48 | 68% | 178 | 166 | 12 | –6 | –50% | 413 | 330 | 83 | 42 | 51% |
| A-P. Horiz. Preop. | 1000 | 185 | 143 | 42 | 30 | 71% | 196 | 151 | 45 | 30 | 67% | 381 | 294 | 87 | 60 | 69% |
| R. Lat. Vert. Postop. | 1640 | 332 | 191 | 141 | 89 | 63% | 308 | 261 | 47 | 2 | 4% | 640 | 452 | 188 | 91 | 48% |
| R. Lat. Vert. Preop. | 1550 | 322 | 211 | 111 | 62 | 56% | 368 | 243 | 125 | 81 | 65% | 690 | 454 | 236 | 143 | 61% |
| R. Lat. Horiz. Postop. | ---- | 329 | 216 | 113 | 96 | 85% | 275 | 266 | 9 | 3 | 33% | 604 | 482 | 122 | 99 | 81% |
| R. Lat. Horiz. Preop. | ---- | 344 | 330 | 14 | 28 | 200% | 362 | 347 | 15 | 13 | 87% | 706 | 677 | 29 | 41 | 141% |

*Planimeter readings in square centimeters from teleoroentgenograms taken in circumstances designated in left-hand column. The second column (Spir.) gives the spirometric reading in cubic centimeters obtained between the taking of the inspiration and expiration films. The next five columns show in order: The internal area of the thorax to the right of the midline on inspiration (Insp.); on expiration (Exp.); the area of excursion of the right lung (Dif.) as given by the difference between the area of inspiration (Insp.) and expiration (Exp.); the excursion of the right diaphragm (Dia.); the ratio of diaphragmatic to total respiration (D/Dif.) obtained by dividing the former (Dia.) by the latter (Dif.). The next five columns show the corresponding values for the left side. The last five columns show the sum of the values for the right and left sides.

Table II, showing the comparison of the diaphragmatic excursion percentage values antepartum and postpartum, was composed from the values given in Table I. In this comparison it is seen that in the case of dolichomorphic I. K. the diaphragmatic excursion percentage is greater antepartum than postpartum both vertically (30 per cent) and horizontally (7 per cent). In the case of brachymorphic E.C.,* the percentage is greater antepartum than postpartum vertically (10 per cent) but less horizontally (–8 per cent). However, the average of the percentages in the two positions reveals an insignificantly greater value for the antepartum state (1 per cent). In the case of H. W. (left phrenic) we again assume that postoperative corresponds to antepartum, and preoperative to postpartum. In the comparison in Table II we see that the diaphragmatic excursion percentage is less postoperative than preoperative both vertically (–16 per cent) and horizontally (–39 per cent). Thus we find that the percentage in a case of left phrenic palsy is diametrically opposed to the percentage in cases of pregnancy.

TABLE II. DIAPHRAGMATIC EXCURSION PERCENTAGE GREATER ANTEPARTUM THAN POSTPARTUM*

| | DOLICHOMORPHIC I. K. | | | BRACHYMORPHIC E. C. | | | H. W. (LEFT PHRENIC) | | |
|---|---|---|---|---|---|---|---|---|---|
| | RIGHT PER CENT | LEFT PER CENT | SUM PER CENT | RIGHT PER CENT | LEFT PER CENT | SUM PER CENT | RIGHT PER CENT | LEFT PER CENT | SUM PER CENT |
| A.-P. Vertical | 15 | 18 | 17 | 12 | 5 | 9 | 13 | –80 | –19 |
| R. Lat. Vertical | 39 | 46 | 43 | 11 | 9 | 10 | 7 | –61 | –13 |
| Aver. Vertical | | | 30 | | | 10 | | | –16 |
| A.-P. Horizont. | 17 | 13 | 15 | 6 | –2 | 2 | –3 | –117 | –18 |
| R. Lat. Horizont. | –19 | 31 | –1 | –13 | –24 | –18 | –115 | –54 | –60 |
| Aver. Horizont. | | | 7 | | | –8 | | | –39 |
| Total Average | | | 19 | | | 1 | | | –28 |

*Diaphragmatic excursion percentage (D/Dif. in Table I) greater antepartum than postpartum for dolichomorphic I. K. and brachymorphic E. C. Under H. W. (left phrenic), the comparison is postoperative greater than preoperative. Negative values indicate the diaphragmatic excursion percentage is greater postpartum than antepartum or greater preoperative than postoperative.

It is interesting to note that in the case of dolichomorphic I. K. the diaphragmatic excursion percentage averages 68 per cent antepartum and 49 per cent postpartum. In the case of brachymorphic E.C. the averages are 70 per cent antepartum and 69 per cent postpartum. H. W. (left phrenic) represents averages of 55 per cent postoperative and 83 per cent preoperative. Thus we find in the planimeter values from our two cases studied antepartum and postpartum that contrary to the general belief the diaphragmatic excursion is greater antepartum than postpartum and that respiration antepartum is more diaphragmatic than costal.

Next we consider the excursion of the costophrenic sinuses and domes of the diaphragm as shown in Table III. In the case of dolichomorphic I. K. we see that the excursion of the costophrenic sinuses in the vertical position is much greater antepartum than postpartum. In the horizontal position, the excursion is greater postpartum than antepartum. However, the excursion of the domes of the diaphragm is greater antepartum than postpartum both vertically and horizontally. The values in the case of brachymorphic E.C. show a greater excursion postpartum

*E. C., (#369887), a healthy white female, aged seventeen years six months, height 155 cm., antepartum weight 66.4 kilograms, was of a brachymorphic habitus. The antepartum studies were obtained twenty-two days before the normal spontaneous delivery of a 3,400 gm. healthy male infant. The postpartum studies were made on the tenth day of the puerperium. This subject is referred to as "brachymorphic E. C." in Tables I, II, III, and IV. The lung outlines from which the data in the tables was obtained are not reproduced for this case as they differed in no essential respect from those shown for 'dolichomorphic I. K.'

than antepartum of the costophrenic sinuses and domes of the diaphragm both vertically and horizontally. In considering the values for H.W. (left phrenic), still assuming that postoperative and antepartum are the comparable states, we find a marked variation from the above two cases. The functioning right diaphragm has a greater excursion postoperatively than preoperatively, but the dome of the paralyzed left diaphragm reveals its paradoxical motion postoperatively by the negative values.

TABLE III. DIAPHRAGMATIC EXCURSION IN MM.*

| | COSTOPHRENIC SINUS | | | | DOME OF DIAPHRAGM | | | |
|---|---|---|---|---|---|---|---|---|
| | RIGHT | | LEFT | | RIGHT | | LEFT | |
| | ANTE. | POST. | ANTE. | POST. | ANTE. | POST. | ANTE. | POST. |
| *Dolichomorphic I. K.* | | | | | | | | |
| Forced Resp. Vert. | 37 | 18 | 49 | 17 | 23 | 12 | 25 | 9 |
| Forced Resp. Horiz. | 49 | 58 | 47 | 48 | 40 | 38 | 34 | 34 |
| *Brachymorphic E. C.* | | | | | | | | |
| Forced Resp. Vert. | 38 | 66 | 40 | 55 | 23 | 31 | 24 | 37 |
| Forced Resp. Horiz. | 54 | 101 | 40 | 63 | 41 | 48 | 33 | 45 |
| *H. W. (Left Phrenic)* | | | | | | | | |
| Forced Resp. Vert. | 57 | 37 | 20 | 48 | 31 | 26 | −6 | 36 |
| Forced Resp. Horiz. | 57 | 38 | 0 | 34 | 41 | 29 | −3 | 27 |
| *K. & B. (Aver. 50 Cases)*[13] | | | | | | | | |
| Forced Resp. Vert. | 37 | 37 | 49 | 34 | 39 | 18 | 52 | 23 |
| Forced Resp. Horiz. | 69 | 65 | 63 | 61 | 51 | 49 | 53 | 47 |
| Quiet Resp. Vert. | 13 | 12 | 13 | 13 | 9 | 8 | 11 | 10 |
| Quiet Resp. Horiz. | 13 | 15 | 12 | 11 | 11 | 11 | 11 | 10 |

*Excursion of diaphragm in millimeters between forced inspiration and expiration measured at the costophrenic sinus and at the dome of the diaphragm on the right and on the left with the subject standing (Vert.) and lying (Horiz.). For dolichomorphic I.K., brachymorphic E. C. and K. and P. (Aver. 50 cases)[13] values for the antepartum (Ante.) and postpartum (Post.) states are given in adjacent columns. For H. W. (left phrenic) postoperative values are given in columns headed Ante. and preoperative values in columns headed Post.

The figures obtained in the above described manner are not to be taken as absolute values. They are of significance only as a basis for relative comparisons. There are many sources of error. The projection of the diaphragm varies if the x-ray tube is not centered at the same level. In outlining the position of the diaphragm within the cardiac shadow it is necessary to be somewhat dogmatic. A true anteroposterior projection can usually be obtained, but this projection gives us information regarding the position of the diaphragm in one plane only. For this reason we made teleorentgenograms with the subjects in the additional projections. It is in these additional projections that the source of error is greatest. In the oblique projections it was impossible to obtain films with the subject in the same degree of rotation, antepartum and postpartum, or vertical and horizontal. Also the delineation of the diaphragm shadow on the oblique projections was uncertain. These difficulties made the determinations for the oblique projections so variable and uncertain that the results were discarded. We also found it difficult to get a true lateral projection. The error caused by a slight

rotation of the subject is most strikingly brought out in the case of H.W. (left phrenic) in the right lateral horizontal preoperative projection (Table I). The inspiratory projection is practically a true lateral but the expiratory film shows some rotation, thus increasing the projection of the A-P diameter and the total area so that it approaches the inspiratory value. The diaphragmatic levels are not proportionately affected by the rotation. As a result the excursion of the right diaphragm as projected is greater than the total excursion recorded for the right side.

In our determinations we have assumed that the postpartum values obtained on the tenth and eleventh days of the puerperium represent the normal nonpregnant state.

This assumption is based on the work of Alward[12] who made daily vital capacity determinations on 60 pregnant women during the last month of pregnancy and during the puerperium. The patients were allowed up on the tenth day and discharged on the fourteenth day of the puerperium. Final determinations were made on the postpartum visit one month to six weeks after delivery. As a result of these observations Alward concluded that "in the majority of cases there is normally a gradual reduction in the vital capacity in the last month of pregnancy. This is especially noticeable during the two-week period before delivery. Following delivery there is a fairly sharp reduction in the vital capacity with a gradual return to normal limits which is reached by the tenth day of the puerperium and remains so throughout the following days of the puerperium."

The spirometric readings obtained between the inspiratory and expiratory exposures varied (Table I). This introduces another source of error. From our data we are unable to say what effect a variation in the spirometric reading has upon the ratio of the diaphragmatic to the total respiratory excursion. In comparing the antepartum and postpartum determinations in our two subjects we find that the several antepartum readings average 1923 c.c.; the postpartum readings average 1943 c.c.

We realize that the data from two cases of pregnancy, especially with the unrefined methods described, would be insignificant if used alone. Therefore we wish to call attention to the work of Klaften and Palugyay,[13] who have performed an extensive investigation.

In fifty women, during the last weeks of pregnancy and up to the tenth postpartum day, they made orthodiagraphic tracings with the subjects standing and lying, during forced inspiration and expiration and quiet inspiration and expiration. From these tracings they obtained vertical measurements from a horizontal line drawn through the midclavicular points to the costophrenic angle and to the dome of the diaphragm on the right and on the left in the four phases of respiration. The measurements thus obtained in the fifty women were averaged. The average values given in the body of the paper by Klaften and Palugyay have been assembled and are presented in Tables III and IV under K. and P. (Aver. 50 cases).

The respiratory movements of the diaphragm were without exception greater antepartum than postpartum as indicated in Table III. On an average, the excursion was greater on the left than on the right (average 48 mm. and 46 mm., respectively), and greater in the costophrenic sinuses than in the region of the domes (average 52 mm. and 42 mm.). The values for quiet respiration in Table III are in accord with Heynemann's statement that there is no essential difference in quiet respiration between the pregnant and puerperal states.

Although values for individual cases are not given, these authors state that the ratio of diaphragmatic and thoracic respiration depends on the constitutional type. The diaphragmatic excursion antepartum and postpartum, and both horizontal (lying) and vertical (standing), was more marked in dolichomorphic than in brachymorphic women. This observation, that the diaphragmatic excursion is greater in dolichomorphic women, is of added interest when we correlate it with the observation that a majority of tuberculous patients are of an asthenic habitus.

The *difference* between the diaphragmatic excursion antepartum and postpartum was more marked in the standing than in the lying position. However, both antepartum and postpartum the excursion of the diaphragm during forced respiration was greater when the subject was horizontal than when vertical. This is of significance, for rest in bed (horizontal position) is the basis for treatment of pulmonary tuberculosis.

TABLE IV. HIGHER POSITION OF DIAPHRAGM ANTEPARTUM THAN POSTPARTUM IN MM.*

| | VERTICAL | | | | HORIZONTAL | | | |
|---|---|---|---|---|---|---|---|---|
| | SINUS | | DOME | | SINUS | | DOME | |
| | RIGHT | LEFT | RIGHT | LEFT | RIGHT | LEFT | RIGHT | LEFT |
| *Dolichomorphic I.K.* | | | | | | | | |
| Forced expiration | 21 | 22 | 19 | 18 | 36 | 28 | 40 | 34 |
| Forced inspiration | 2 | –10 | 8 | 2 | 45 | 29 | 38 | 34 |
| *Brachymorphic E.C.* | | | | | | | | |
| Forced expiration | 14 | 11 | 15 | 9 | 24 | 27 | 28 | 22 |
| Forced inspiration | 42 | 26 | 23 | 22 | 71 | 50 | 35 | 34 |
| *H.W. (Left Phrenic)* | | | | | | | | |
| Forced expiration | 13 | 10 | 4 | –10 | –43 | –5 | –11 | –3 |
| Forced inspiration | –7 | 38 | –1 | 32 | –62 | 29 | –23 | 27 |
| *K. & P. (Aver. 50 Cases)*[13] | | | | | | | | |
| Forced expiration | 29 | 18 | 16 | 14 | 21 | 16 | 16 | 12 |
| Forced inspiration | 29 | 3 | 5 | –17 | 16 | 14 | 14 | 6 |
| Quiet expiration | 28 | 15 | 16 | 11 | 24 | 19 | 18 | 14 |
| Quiet inspiration | 27 | 15 | 15 | 10 | 26 | 18 | 18 | 13 |

*Higher position of diaphragm antepartum than postpartum in millimeters at the costophrenic sinus and dome on the right and on the left. For H. W. (left phrenic) the comparison is higher postoperative than preoperative. Negative values indicate higher postpartum than antepartum or higher preoperative than postoperative.

In Table IV we see that the diaphragm is higher antepartum than postpartum, being much more so on forced expiration than on forced inspiration. Under K. and P. (aver. 50 cases) the value for forced inspiration at the left dome of the diaphragm is –17 mm. This is surprising for it means that the left dome of the diaphragm on forced inspiration in the vertical position is lower antepartum than postpartum in spite of the gravid uterus.

## SUMMARY

One of the arguments frequently given for the conservation of pregnancy in a tuberculous patient is that the gravid uterus elevates the diaphragm and acts as a splint, thus giving the effect of a phrenic nerve interruption. However, the work of Heynemann, the work of Klaften and Palugyay, and our observations show that the diaphragm on expiration is higher antepartum than postpartum, but on inspiration the diaphragm descends to a level that is more nearly comparable to that of the puerperal state. Therefore, in pregnancy, the diaphragm, instead of being splinted, tends to have a greater excursion on forced respiration than in the nonpregnant state. In contradistinction to this the paralyzed diaphragm ascends on inspiration, and it is only this paralyzed diaphragm that has been shown to be of value in pulmonary tuberculosis. The actively functioning diaphragm, though high in position, has never been demonstrated to be of value in pulmonary tuberculosis. Therefore,the hypothesis that tuberculosis may be benefited by the effect of pregnancy on the diaphragm is not justified.

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# WHEAT GERM OIL THERAPY

## I. Dosage—Idiosyncrasy

Evan Shute, B.A., M.B., F.R.C.S.C., London, Canada
*(From the Department of Obstetrics and Gynecology, University of Western Ontario)*

VERY little has appeared in the literature on the practical problems involved in wheat germ oil therapy. A rational basis for dosage, some indication of the variations in dose demanded by different types of cases, what dosage if any is excessive, whether idiosyncrasies occur, all of these points require elaboration. How long will wheat germ oil retain its potency unchanged and what are the optimal conditions for its preservation? What is its effect upon the onset and duration of normal labor if it is administered until labor begins at term? Are there pathologic processes other than habitual abortion in which it is of value, and where failures occur, to what should they be ascribed? These problems are examples of those that remain to be studied.

It is in the hope of throwing some light into these corners that the following analysis of clinical experiences with a group of 115 female and 12 male patients is presented. A dozen or so of these have been already included in the Watson and Tew report[1] on the influence of wheat germ oil therapy on abortion.

### DOSAGE

There seems to be no general agreement about the dosage of wheat germ oil required by patients of various clinical types.

Early in the experimental work on the subject, Evans and his coworkers[2] determined the minimal single dose of the oil which would protect an E-free rat from resorbing or aborting its young. Various other authorities, Juhasz-Schaffer,[3] Sure,[4] and Gierhake[5] have similarly estimated this rat dose using various oils and concentrates. However, such estimates have relatively little value in deciding upon the dosage to be administered to human patients. The first workers[6] in the clinical field in most cases used 2 to 3 gm. as the daily dose from the time treatment was begun. No precautions as to storage or the variations in individual requirement were urged in their reports. So far as we can discover, there has never been any precise indication for quantitative dosage given except that mentioned in an earlier publication of ours.[7]

We stated that sufficient wheat germ oil should be given to render the blood serum of the patient under consideration normally digestible by a dilute trypsin solution under the precise conditions of the test we had elaborated.[8] It was found that many women threatening to abort would not do so if given a single massive dose of the oil, supplemented by smaller daily doses thereafter. The usual initial dose required was

6 dr. or more, and within approximately twenty hours of its administration the antiproteolytic factor related to the onset of abortion disappeared from the blood serum. This factor was later proved to be an estrogenic substance.[9, 10] Its disappearance from the serum coincided with subsidence of the symptoms and signs of abortion. If none but the initial dose were given the antiproteolytic estrogenic factor reappeared in the serum on the average in four days or a little more, and simultaneously symptoms and signs of impending interruption of pregnancy might or might not recur promptly. It therefore became our routine to administer within the first twenty-four hours of therapy three doses, each of 4 dr., of wheat germ oil (roughly twice the minimal dose required), and to follow this with 1 dr. of oil each day.

It should be understood that the oil used was at first a fresh ether-extracted wheat germ oil, kept in a refrigerator until and during use. In the past year and a half a cold pressed oil has been used in its stead. Its dosage appears to be the same.

We have not undertaken any extended clinical or laboratory analysis of any of the other wheat germ oils now on the market. The oil used has been prepared by a standardized technique but has not been standardized pharmacologically. It was known to possess fairly consistently a satisfactory content of vitamin E. Not only has it remained effective in clinical cases, many of which are always under observation and are periodically checked for the reappearance of antiproteolysis in their serums, but it has been checked repeatedly on E-free rats during the past two years. The early workers with wheat germ oil have pointed out that some wheat germ seems to be quite defective in vitamin E content. The reason is as yet unknown.

Bacharach[11] has recently pointed out that it is very doubtful if there can be a standard preparation or a unit of vitamin E, for no biologic standardization is possible. It certainly does not seem to be commercially feasible to standardize a wheat germ oil of the type used by us. To do so would entail its administration to a group of E-free rats in such quantities and under such controlled conditions as would ensure a pregnancy carried to a successful conclusion. This would require twenty-one days on the average. For reasons to be given later it appears that the length of time during which wheat germ oil remains potent is little more than eight weeks even when kept under optimum conditions. There would, in short, be only five weeks during which animal-standardized samples of the oil could be distributed and sold. This would scarcely be practicable.

There has been accumulating recently a most interesting body of evidence to indicate that there are enormous variations in the capacities of different individuals to assimilate the various known vitamins.

Moncrieff[12] reported the development of scurvy in a child receiving a diet adequate in vitamin C and rickets appearing similarly on a diet adequate in vitamin D. Thatcher,[13] on the contrary, reported fatal hypervitaminosis D occurring on a dietary containing a not unusually large intake of cod liver oil. Ayad[14] cited the case of a man unharmed by a prodigious intake of cod liver oil over a period of six years, and several other cases unharmed by huge doses of vitamin D over a considerable period of time. Moreover, as regards vitamin $B_1$, Baker and Wright[15] have indicated that beriberi may develop on a diet containing anything from 71 to 382 international units (indeed that it occurs in Ireland on a diet containing 438 units), that there is a distinct difference in the minimal requirement of Europeans and natives in the Dutch East Indies, and that during pregnancy, in experimental animals at least, the requirement rises three to five times. Jeans and Zentmire[16] working with vitamin A and Gothlin and his coworkers[17] with vitamin C have demonstrated that a large proportion of the population of various countries exists in a chronic state of hypovitaminosis hitherto unsuspected.

It would seem, therefore, that contrary to the opinion of Sure[18] and some other authorities, we might suspect the existence of a state of hypovitaminosis in respect to vitamin E in people living apparently normally on the mixed dietary of Canada and the United States. As Vogt-Miller[19] also has observed, similar rats identically fed become E-defective on a diet deficient in vitamin E after varying intervals of time.[7] He early pointed out that women in Denmark on ordinary diets could not be suspected a priori of E deficiency. Yet he admitted that a few women might require more of this vitamin than did the average. Similarly we have found large differences in the amount of wheat germ oil required to nullify the effects of E-deficiency in the human being. The largest daily dosage required to date has been twenty-four drams of wheat germ oil a day. A point we should like to stress is that if the patient requiring a large dose received anything short of that dose, she derived very little benefit from it. She went on to display most of the symptoms which would show themselves had no treatment been instituted. As we understand it, the major requirement of such therapy is that it should be sufficient to remove the estrogenic antiproteolytic factor from her blood serum, as evidenced by the author's test, and hold it in abeyance.

When one considers the large number of wheat germ oils now on the market, the question of "quality versus quantity" in matters of dosage must arise. There appears to be a different requirement in each case, depending on the varying concentration of the antiproteolytic estrogenic factor in the blood and the amount of vitamin E actually present in any wheat germ oil preparation used. Since these factors are so variable, we feel that there is need of a standard of saturation, by which one may know when the particular patient under consideration at the particular stage of pregnancy she has reached at the moment, is brought under control with the particular kind and batch of wheat germ oil used. Quality is more important than quantity, obviously, and determines the latter. Hence the significance of the criterion of dosage for each in-

dividual that we have proposed.[7] Neglect to observe the variations in the requirement of wheat germ oil probably explains many or most of the "failures" occurring in patients under treatment with it. So frequently, when our study was in its early stages, did we find patients continuing to bleed and threatening to abort or miscarry on the continuing dosage of one dram per day that we came to rely upon our serologic test for the control of the patient. Otherwise the first indication of an inadequate continuing dose would occasionally present itself in the form of ruptured membranes. The most appropriate index for treatment at the moment appears to be the disappearance of the antiproteolytic estrogenic factor from the blood serum.

When large doses were first employed, there was some anxiety lest they prove toxic. However, both Juhasz-Schaffer and Evans and Burr had established the fact that no bad effects could be discerned in rats given much larger doses than they usually required. Our clinical experience has amply demonstrated the safety of large doses. We have treated many women with 4 to 6 dr. of wheat germ oil each day for months, and one woman took three ounces each day for two months. In no case was any untoward effect observed. Watson and Tew[1] have also stated that doses as high as 20 c.c. per day were not observed to have any harmful influence. It should be pointed out, however, that the great majority of women are adequately controlled by the usual initial dose of 6 to 12 dr., followed by 1 dr. each day.

It is worthy of comment that in almost every instance in which an unusually large dose of wheat germ oil has been required for the preservation of pregnancy, the patient has been a case of hypothyroidism. It may be, of course, that this study was conducted in an area in which a very large proportion of such cases was present—indeed, we have felt that such was the case. Whatever the explanation is, the fact has been very impressive. These hypothyroid women appear either to manufacture great excesses of the estrogenic antiproteolytic factor or to be unable to excrete it adequately. That the latter may prove to be the correct alternative is suggested by the animal work of Van Horn,[20] and of Weichert and Boyd.[21] Benazzi[22] also illustrated the relationship between estrin and the thyroid gland by injecting rats with estrin and producing marked thyroid hypoplasia.

Up to the present we have found 39 individuals who required a maintenance dose of the oil of at least triple the usual daily 1 dr.; of these three had basal metabolic rates before pregnancy of between 13 and 20 per cent below normal. None of the remaining 36 had had basal metabolic rates taken, but 25 of the 36 had had definite symptoms and signs of hypothyroidism such as antegestational menorrhagia, poor cold tolerance, great fatigability, constipation, and dry skin. These symptoms were promptly controlled by doses of thyroid extract and recurred in whole or in part when the thyroid extract was discontinued. Indeed

we were able in three patients to render the patient's blood serum free of this antiproteolytic factor by means of the administration of thyroid extract alone.

### IDIOSYNCRASY

We have seen five adult patients and one infant who have evinced signs of sensitivity to wheat germ oil.

One patient was a case of chronic asthma and recurrent hay fever, very highly allergic to many plant and animal proteins. In the course of routine tests done some years before she had been found sensitive to wheat. On three occasions a massive dose of ether-extracted wheat germ oil controlled threatened abortions and a maintenance dose of 4 dr. of the oil was required each day for a fortnight. With each compulsory return to the medication she developed increasing flatulence with nausea and vomiting. A period of one month elapsed during which no oil was administered. When it was given again, the above-mentioned symptoms were more marked than ever and very distressing. It was found necessary to discontinue the wheat germ oil therapy for a time, at least, and use one of the concentrates on the market. This produced less flatulence but still there was a great deal of it. She experienced the same generalized cutaneous "pricking" sensation with the concentrate as with the oil, and remarked that she had experienced this curious cutaneous sensation after the ingestion of certain foods, such as onion, to which she is allergic also. She chose to return to the oil therapy but this time a cold-pressed oil was used. Three weeks later, generalized pruritus forced her to stop. Near the end of her pregnancy, albuminuria and a rising blood pressure compelled her to return to the cold-pressed oil therapy. At once her nausea and extreme abdominal distention returned, rendering her so constantly uncomfortable that again the oil was discontinued. Labor was induced satisfactorily.

Another patient seen recently was a woman aged sixty years whose menopause developed six years ago. For the past three years she had had intense vaginal pruritus and vaginitis. The vaginal mucosa was raw, red, and acutely tender. No complicating parasitic infection nor glycosuria could be discovered. As a blood test revealed an excess of the estrogenic antiproteolytic factor she was given thyroid extract in the hope that it would remove the estrogenic substance from the blood. However, she proved intolerant of such therapy, for it produced tachycardia, palpitation, sweats, and insomnia. Then she was given ether-extracted wheat germ oil in the usual massive dose and carried along on 2 dr. each day. All her pruritus soon ceased and the raw red vaginitis disappeared in about four days. She remained improved for about two months, except for a monthly exacerbation of her pruritus for a period of approximately five days on each occasion. At the end of that time she had a bout of influenza and stopped taking her wheat germ oil while taking a good deal of other medication. When she returned to it, she experienced a sensation of intense "waves of heat" spreading all over her body and promptly displayed a generalized urticarial skin eruption. This was ascribed to strawberries, although that fruit had never affected her similarly before. She stopped her wheat germ oil therapy and promptly lost her sensations of heat and her rash; returning to treatment with cold-pressed wheat germ oil at once brought back her two complaints of heat and urticaria. At present she is unable to continue the use of wheat germ oil and her vaginitis is as troublesome as ever. We attempted to have this patient tested for sensitivity to wheat but this has been refused, and she has sought other medical advice.

The third case was a primipara, thirty-one years old. There was no family nor personal history of allergic sensitivity. She gave a history of poor heat tolerance

and excessive perspiration when first seen. Although extremely ruddy, her hemoglobin was only 57 per cent Sahli. She early developed evidences of toxemia of the abruptio placentae type[23] and this was controlled by an adequate dosage of ether-extracted wheat germ oil. She continued to gain weight rather excessively but her blood pressure was kept within bounds by a dose of as much as 8 dr. each day. After two months she experienced severe hot flashes lasting about five minutes each time and these recurred many times each day. She suffered from an unusually hot summer in a pitiable way. Finally, three months after her oil therapy had been instituted, she developed a generalized, raised, blotchy, reddish, discrete rash which was at times very itchy. She was tested for sensitivity to wheat by skin testing. (Courtesy of my colleague, Dr. Gordon Calder.) The wheat injection promptly produced an area closely resembling one of the blotches of her rash. Accordingly, her wheat germ oil therapy was discontinued and she was given a concentrate of the same marketed by another company. Her rash promptly disappeared, but such a huge dosage was required to control her toxemia and the antiproteolytic factor in her blood that the expense of the treatment was prohibitive. She reverted to the bulk oil therapy, but used a cold-pressed rather than an ether-extracted oil. There was a very slight flare-up of the rash and pruritus but never enough to render her unwilling to continue the use of this preparation. She took it till term, then stopped, and her rash and pruritus ceased in three days.

The other two instances in adults were not so striking but were definite. One woman developed a rash and the other an urticaria. Both were intensely itchy. The infantile sensitivity was noticed in a baby whose mother required wheat germ oil to effect lactation. During the whole period of time when the mother was treated with the oil, a matter of two weeks, the infant had numerous yellow stools filled with minute bubbles and containing a moderate proportion of clear mucus. Within two days of the cessation of the oil, the infant's stools became normal and remained so. The mother took four drams of the oil once again, when the child was three months old. The following day the child had a return of the characteristic stool, which remained as it was for a day, then reverted to normal. When the mother was not taking the oil, the child, which is now over five months old, never had anything but a perfectly normal stool.

## SUMMARY

1. The most suitable routine dosage of ether-extracted or cold-pressed wheat germ oils of the type with which we have worked proved to be 12 dr. inside of the first twenty-four hours of treatment, followed by at least 1 dr. each day. The dosage varied with individual requirement, the quality of the oil used, and the stage of pregnancy.

2. A state of hypovitaminosis E appears to be relatively common among the pregnant women of this country.

3. Enormous doses of wheat germ oil seem to produce no untoward symptoms.

4. Of 39 women requiring huge doses of wheat germ oil, 28 were hypothyroid cases.

5. Six instances of idiosyncrasy to wheat germ oil are recorded.

NOTE.—In view of the recent report by Rowntree and others (Am. J. Cancer 31: 359, 1937) on the sarcogenic properties of crude ether-extracted wheat germ oil in rats, it should be pointed out that our study of patients treated with wheat germ oil was begun nearly four years ago.

For the first two and one-half years, an ether-extracted oil was used, since that only a cold-pressed oil. Of the 127 patients one has developed malignancy. She revealed chorionepitheliomatous change in what was grossly an hydatid mole found ten months after the termination of a pregnancy in which she had been given an ether-extracted wheat germ oil in small doses for the final six weeks.

Rowntree's report suggests a certain species specificity in the rat for his oil-produced tumor. He and his colleagues did not find such tumors produced with cold-pressed wheat germ oil. Moreover they found the tumors developed in the susceptible species only upon administration of oil containing sediment and when the oil was given in doses enormously greater in proportion to weight than have ever been fed to human beings. As rancidity, which rapidly destroys vitamin E, did not affect the sarcogenic power of their oil, it appears that the vitamin itself cannot be blamed for the production of the neoplasms.

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**Hees, E.: Ascending Trichomonas Vaginalis Infection,** Gynéc. et obst. **34:** 191, 1936.

*Trichomonas vaginalis* locally infects the vagina. Without appropriate specific therapy, however, a progressive ascending infection of the genital tract ensues with the flagellates following the endometrium and the endosalpinx, or the lymphatics. Such upper genital tract infection rarely causes temperature elevations higher than 39° C.

Pelvic abscesses caused by *trichomonas vaginalis* are not rare. They are characterized by extensive and very dense adhesions. The histologic picture in adnexal disease caused by *trichomonas vaginalis* is not specific and resembles that seen in chronic purulent salpingitis.

The author states that by microscopic examination and by culture it has been possible to determine the presence of trichomonas in human sperm, endometrium, chronically inflamed tubes, ovarian cysts, the peritoneum, the blood stream of patients, and the viscera of the fetus.

Arnold Goldberger.

# FETAL AND MATERNAL MORTALITY IN DIABETES*

EDITH L. POTTER, PH.D., M.D., AND FRED L. ADAIR, M.A., M.D.,
CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)*

PRIOR to the discovery of insulin, agreement was uniform that pregnancy constituted a dangerous and undesirable complication of diabetes mellitus. The literature before 1923 is filled with discussion and case reports concerning the harmful effect produced by pregnancy. Few diabetic women bore children (pregnancies in 2 per cent, 5 per cent, 6 per cent of diabetic women of childbearing age as reported by Skipper, Van Noorden, Lecorche), but when a patient did become pregnant her diabetes became more difficult to control, she was very likely to develop acidosis and her chances of surviving the pregnancy were much less than for normal women. The likelihood of obtaining a liveborn infant capable of surviving the neonatal period was less than 50 per cent. The cause of the high fetal death rate was due to many factors. Spontaneous abortions in the early months were attributed to an abnormal endometrium, to variations in maternal blood sugar or to ketosis. Therapeutic abortions were necessitated by increased difficulty in controlling the blood sugar level in the presence of pregnancy. Hydramnios was a frequent occurrence (12 of 66 pregnancies in diabetes collected from the literature by Williams in 1909) and was usually associated with death of the fetus (83 per cent of Williams' 12 cases). The excessive development which frequently occurred if the fetus survived until term was responsible for a greater incidence of intracranial injury than occurs in infants of normal size. A higher incidence of malformations in infants born of diabetic mothers was reported by Joslin, but has not been corroborated by other investigators. Ketosis and abnormal products of metabolism circulating in the mother's blood were regarded as frequent causes of intrauterine death. Hypoglycemia after birth, caused by an overly active fetal pancreas, developed in response to low maternal pancreatic function, was considered a frequent cause of death in the early neonatal period.

One of the first large series of cases of pregnancy in diabetes mellitus collected from the literature was reported by Williams in 1909. In this group of 66 pregnancies, 57 occurred in diabetic women and the first symptoms of diabetes developed after conception occurred in 9. Contrary to more recent observations the mortality was higher in the latter group than in the first. Of the 9 patients with the onset

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of diabetes during the pregnancy 3 died in coma shortly after labor, 2 died of coma at one and at four months later, 2 died of malignant tumors shortly after labor. Death from diabetes occurred in 55 per cent. Only 3 infants survived, two from mothers who also survived and one from a patient who died of a brain tumor. In the 26 patients (57 deliveries) in whom diabetes was present before conception the mortality during the puerperium was 25 per cent, during the next two years 20 per cent, with a fetal mortality of 49 per cent. Ten of these patients had more than one pregnancy, 6 being apparently entirely unaffected by repeated pregnancies.

Joslin observed 130 pregnancies occurring in diabetic women before the insulin era. Seventy-one per cent of those proceeding to term, in whom the outcome of the pregnancy was known, resulted in liveborn infants. However, from a total of 115 pregnancies (the outcome was unknown in the other 15) there were obtained only 57 live infants (50 per cent). There were 23 stillbirths, 23 abortions and miscarriages, 5 therapeutic abortions, 7 deaths because of deaths of undelivered mothers. The maternal mortality is given as 5 per cent, all deaths being due directly to diabetes.

Since the advent of insulin many more cases have been reported in which diabetes complicates pregnancy.

Fischer believes this indicates that more diabetic women are becoming pregnant. This belief is supported by Skipper's figures which show that of 367 married diabetic women under forty-six years of age only 2 per cent of 190 observed prior to 1922 were pregnant, while 15 per cent of 177 observed since 1922 were pregnant. In spite of the fact that early diabetes is probably recognized more frequently than it was in the past, these figures show that the fertility of a diabetic woman is probably increased by insulin.

Wilder and Parsons (1928), in their study of the effect of pregnancy on diabetes, state that in their experience no patient is permanently harmed by pregnancy if the disease is properly treated. They report 9 cases of pregnancy in diabetes with 6 living children (66⅔ per cent). The deaths include one infant stillborn at term in a case of neglected diabetes, and 2 abortions at two and seven months from coincidental causes. There was no maternal mortality. An investigation of 51 published case histories from 1923 to 1928 shows 57 per cent living babies with a maternal mortality of 13.7 per cent (7 deaths).

Skipper (1933) reports 37 pregnancies in 33 women with a fetal mortality of 40.5 per cent (including 3 therapeutic abortions), with no maternal mortality during labor or the puerperium and with but one death inside of two years. His figures, collected from the literature on 136 pregnancies in 118 women, show a fetal death rate of 45.2 per cent (abortions, stillbirths, neonatal deaths) and a maternal death rate of 9.3 per cent during pregnancy or the puerperium, with an additional 3.4 per cent dying within two years after delivery.

Ronsheim, between 1920 and 1933, observed 36 pregnancies in diabetic women with only 13 live births (36 per cent), the deaths including 8 therapeutic abortions, 13 stillbirths, and 2 miscarriages. There was only one maternal death. He states that uncontrolled diabetes invariably results in miscarriage, premature birth, or death in utero a few weeks before term. Cesarean section a few weeks before term may occasionally be indicated in the interest of the patient.

Duncan and Fetter (1934) report 6 pregnancies in 5 diabetic women with no fetal or maternal mortality.

Kramer (1935) in 17 patients with 20 pregnancies observed no maternal deaths during pregnancy or the puerperium and only one within two years. He states

there were 5 abortions, including 2 therapeutic, but does not give the number of live births. He has collected 238 cases from other authors in which there were only 114 infants alive three days postpartum (50 per cent). There were 8 maternal deaths during the puerperium, 17 within one year and 19 up to three years, making a total of 14.2 per cent.

Joslin's series of cases (1935) is the largest reported by a single investigator since insulin has been available and consists of 122 pregnancies in which the outcome is known. In only 57 per cent of the cases did the fetus survive. If 13 therapeutic abortions are excluded, the percentage rises to 70 per cent (live births 70, stillbirths 19, miscarriages or abortions 19, therapeutic abortions 13, ectopic pregnancy 1). In 73 patients under Joslin's immediate care the number of live births is 68 per cent, or 75 per cent if 7 therapeutic abortions are excluded. The maternal death rate of 5 per cent is the same as in the pre-insulin era but the cause of death has changed from diabetic coma to obstetric complications. He believes that cesarean section in the early part of the eighth month is the ideal method of delivery.

Since the opening of the present Chicago Lying-in Hospital at the end of May, 1931, until Oct. 1, 1936, 16 pregnancies in 15 women having proved diabetes mellitus have been observed. There have been a total of 14,464 deliveries during this period, making an incidence of approximately one in every 900 deliveries. Eleven women had had symptoms of diabetes for at least two years before the onset of pregnancy, in three it developed during the course of the pregnancy, and in one case the time of onset was unknown. There was only one maternal death (6.6 per cent). This occurred in a woman admitted to the hospital in coma, who had had no prenatal care and who died undelivered a few hours after admission. There were 11 infants (68.7 per cent) alive at the end of the neonatal period. The fetal deaths were due to one therapeutic abortion performed because of the acidosis produced by hyperemesis gravidarum; to one delivery of a macerated stillborn infant in a woman with poorly controlled diabetes; one premature onset of labor at thirty-one weeks due to an unknown cause in which the infant succumbed six hours after delivery, one death of an undelivered infant, and to one death of an infant showing evidence of antenatal pneumonia as a result of premature rupture of the amniotic membranes.

In general, the age when pregnancy occurred is slightly greater than usual, the average age in this group being thirty years. Seven women (50 per cent) showed evidence of toxemia, 5 having relatively mild symptoms and 2 having very severe symptoms. Delivery was natural or aided by low forceps in 7, accomplished by cesarean section in 5; one patient died undelivered and one was subjected to a therapeutic abortion. In the 5 patients delivered by cesarean section the diabetes was considered sufficiently severe to warrant sterilizing the patient at the same time.

The mean weight of the infants delivered at term was 3,935 gm., and the sexes were equally divided. There were no fetal malformations.

The patients were all carefully observed during pregnancy and were, with one exception, very cooperative. The one patient who was delivered

of a macerated infant found it very difficult to adhere to an accurately planned diet because of financial embarrassment. With the exception of two patients insulin was given during all or the greater part of the pregnancies.

## DISCUSSION

Since the advent of insulin the entire management of diabetes has changed. It is no longer invariably fatal even when the onset of the disease is in childhood. The surgical risk to the patient has been markedly lowered, and the average diabetic patient who follows the advice of a competent physician has a life expectancy not greatly below that of the nondiabetic individual. The diabetic patient's reaction to pregnancy must necessarily also be modified by the present accessibility of insulin.

The varying nutritive requirements during pregnancy make it imperative that a diabetic patient be more closely supervised than is otherwise necessary. If her blood sugar level is not constantly controlled by diet and insulin, her outlook is no better than it would have been in the preinsulin period. Hyperemesis gravidarum may make it impossible to prevent acidosis in a diabetic patient and is a more serious complication than in a nondiabetic. This is one of the few conditions in diabetes in which therapeutic abortion may be necessary.

The published opinion of various writers differs as to the possible effect of pregnancy on the mother, but from a careful study of many of the cases reported, it seems warranted to draw the following conclusions. Pregnancy constitutes an additional strain on an organism already handicapped by an abnormal sugar metabolism. As in any disease, unnecessary additional factors constituting in themselves a risk to the patient are to be avoided if possible. For this reason, if no other conditions are taken into account, pregnancy is to be avoided. If, on the other hand, the patient is anxious to bear children and is able to have her dietary and insulin requirements carefully controlled, there is no evidence to indicate that she will be certainly and permanently harmed by the pregnancy. Death from coma, which was the usual cause in preinsulin days, is extremely uncommon. (Joslin observed none in 138 pregnancies.) There is a slightly greater risk of toxemia or eclampsia occurring, for the incidence is higher in diabetic than nondiabetic patients, but appropriate treatment may be instituted. Here, as in all patients, careful observation and the discovery of the impending toxemia is the important factor in preventing casualties.

The number of fetal deaths in the series of cases compiled from the literature remains high (see Table II). This is partly due to the inclusion in the statistics of all abortions and miscarriages both uninten-

TABLE I. PREGNANCY IN PATIENTS WITH DIABETES MELLITUS OBSERVED AT THE CHICAGO LYING-IN HOSPITAL

| | DATE OF DELIVERY | AGE AT DELIVERY | DURATION OF DIABETES | SEVERITY OF DISEASE | INSULIN | MODIFIED DIET | TYPE OF DELIVERY | COMPLICATIONS | PREVIOUS PREGNANCIES | | FETUS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | BEFORE DIAGNOSIS | AFTER DIAGNOSIS | SEX | WEIGHT IN GRAMS | STATE |
| 1 | 1931 | 27 | 5 yr. | Sev. | + | + | Ces. sec. steril. | Mod. hypertension | 0 | 0 | F | 3,010 | Normal |
| 2 | 1932 | 23 | 2 yr. | Sev. | + | + | Ces. sec. steril. | Yeast infection; pre-eclampsia; hydramnios | 1 LB | 0 | M | 4,550 | Normal |
| 3 | 1932 | 30 | 5 yr. | Mod. | + | + | Spont. | Preeclampsia | 0 | 0 | F | 4,015 | Normal |
| 4 | 1933 | 36 | 10 yr. | Sev. | + | + | Spont. | Diabetes poorly controlled | 1 LB | 1 SB<br>1 LB | F | 3,945 | Stillborn; macerated |
| 5a | 1934 | 36 | 2 yr. | Mod. | + | + | Spont. | Syphilis (latent); hypertension | 4 LB | 1 Ab | F | 4,000 | Normal |
| 5b | 1935 | 37 | 3 yr. | Mod. | + | + | Ces. sec. steril. | Syphilis (latent); hypertension; yeast vaginitis; preeclampsia | 4 LB | 1 Ab<br>1 LB | M | 4,685 | Normal |
| 6 | 1934 | 38 | Preg. | Mild | 0 | + | Spont. | Mild toxemia | 1 LB<br>5 Ab | 0 | F | 3,610 | Normal |
| 7 | 1934 | 22 | Unknown | Sev. | + | - | Undel. | Toxemia | 1 LB | 0 | F | ? | Died undel. |
| 8 | 1934 | 26 | 6 yr. | Mild | + | + | Low forc. | Mild toxemia | | 1 Ab | M | 3,470 | Normal |
| 9 | 1935 | 30 | 8 yr. | Sev. | + | + | Ces. sec. steril. | None | 2 LB | 1 LB<br>2 Ab | M | 3,925 | Normal |
| 10 | 1935 | 29 | 10 yr. No symptoms for 9 yr. | Mild | + | + | Spont. 31 wk. | Premature onset of labor | 0 | 0 | M | 1,820 | Lived 2 hr. |
| 11 | 1936 | 35 | 4 yr. | Mod. | + | + | Ces. sec. steril. | Preeclampsia | 1 LB | 0 | F | 4,320 | Normal |
| 12 | 1936 | 34 | 4 yr. | Sev. | + | + | Ther. ab. at 2 mo. | Hyperemesis gravidarum | 0 | 0 | - | - | - |
| 13 | 1936 | 22 | Preg. | Mod. | + | + | Low forc. | None | 0 | 0 | M | 3,665 | Normal |
| 14 | 1936 | 17 | Preg. | Mild | 0 | 0 | Low forc. | Well compensated mitral stenosis | 0 | 0 | M | 3,330 | Normal |
| 15 | 1936 | 36 | 3 yr. | Mod. | + | + | Embryotomy | Obesity | 1 Ab | 2 Ab | M | 3,510 | Stillborn; pneumonia |

LB=Normal live born infant.
SB=Still-born infant.
Ab=Abortion.

tional and therapeutic. Adair and other investigators have found that among women in general approximately one-third of all pregnancies end in abortions. The incidence is not greater than this in diabetes, so although we may in this group ascribe a reason for the abortion where ordinarily it is very difficult, the incidence in general is no higher than among women in the nondiabetic group.

TABLE II. PUBLISHED MATERNAL AND FETAL MORTALITY RATES IN DIABETES MELLITUS

| | YEAR PUBLISHED | NUMBER PATIENTS | NUMBER PREGNANCIES | *FETAL MORTALITY % | MATERNAL MORTALITY PER CENT | | |
|---|---|---|---|---|---|---|---|
| | | | | | DURING LABOR | FOLLOWING 2 YEARS | TOTAL |
| Williams | 1909 | 43 | 66 | 49.0 | 25.0 | 20.0 | 45.0 |
| Joslin | 1935[1] | | 115 | 50.0 | 5.0 | | 5.0 |
| Parsons and Wilder | 1928 | 9 | 9 | 33.0 | | | |
| Parsons and Wilder† | | 43 | 51 | 47.0 | | | 12.0 |
| Skipper | 1933 | 33 | 37 | 40.5 | | 3.03 | |
| Skipper† | | 118 | 136 | 45.2 | 9.3 | 3.4 | 12.7 |
| Ronsheim | 1933 | | 36 | 64.0 | 2.8 | | 2.8 |
| Duncan and Fetter | 1934 | 5 | 6 | | | | |
| Kramer | 1935 | 17 | 20 | | | 5.0 | 5.0 |
| Kramer† | | | 238 | 50.0 | | | 14.2 |
| Joslin[2] | 1935 | | 122 | 43.0 | | | 5.0 |
| Chicago Lying-in Hospital (present series) | 1936 | 15 | 16 | 31.3 | 6.6 | | |

*Includes abortions both spontaneous and therapeutic, stillbirths and deaths during neonatal period.

†Cases collected from the literature by the author.

[1]Cases observed prior to the use of insulin (1922).

[2]Cases observed from 1922 to 1935.

If the deaths of previable fetuses are excluded in the Chicago Lying-in series, there are only 3 deaths in 14 pregnancies, a mortality rate of 21.4 per cent. In 81 patients under Joslin's immediate care, 88 per cent of infants delivered at term were liveborn.

In the infants surviving until term the outcome depends largely on the degree to which the maternal diabetes has been controlled. If the patient's urine has been kept relatively sugar-free by diet and insulin and acidosis has not occurred, a live-born infant, within normal limits of size, will probably be delivered naturally. If the diabetes has not been controlled, the outlook is the same as it was in the pre-insulin era; the infant may succumb before delivery and may show maceration of varying degree, it may attain an abnormal size and die as a result of birth trauma, or it may be apparently normal at the time of delivery and succumb soon afterward. Death shortly before labor is probably due in the majority of cases to transmission from maternal to fetal circulation of abnormal metabolic products which interfere with the normal physiology of the infant. Abnormal size of the infant is believed due

to the increased amount of available food material occasioned by the maternal hyperglycemia. Fischer (1935), in analyzing birth weights of 49 infants born of diabetic mothers prior to 1922, found 26 (53 per cent) weighing over 4,500 gm. In 31 infants born of diabetic mothers treated with insulin, there were only 5 which weighed 4,500 or more grams (16 per cent). In none of the patients was pregnancy prolonged. (Kaern, in analyzing 26,644 unselected births, found an incidence of only 0.92 per cent with a birth weight over 4,500 gm. and in half of these the period of gestation was over 291 days.) In all infants over 4,500 gm. the death rate is considerably higher than in those whose weight is within normal limits.

Hypertrophy of the islands of Langerhans in the fetal pancreas, caused by insufficiency of maternal insulin, has been reported by several investigators (Gordon, Heiberg, Skipper, Dubreuil and Anderodias, Feldman, Ambard, Wiener). Whether or not insulin passes through the placenta into the maternal blood stream and thereby partially compensates for the lack of insulin in the maternal organism has not been definitely proved. The hypothesis that after birth the excess of insulin, no longer being able to escape through the placental circulation, is sufficient to cause hypoglycemia and death of the fetus is an interesting possibility. It is almost impossible to estimate accurately the island tissue in the fetal pancreas. In one case discovered by us in routine autopsy investigation, the fetal pancreas was composed largely of islands, all of which were several times the normal size. The infant succumbed from pneumonia and the mother showed no evidence of diabetes.

Positive knowledge as to the cause of death in the infants born of diabetic mothers is still lacking. This is partly because any investigator has the opportunity of studying only a limited number of cases, and partly because the cause of death is largely from physiologic disturbances and does not produce demonstrable pathologic lesions.

As the general care of the diabetic patient is improved, the fetal death rate will decrease correspondingly. The diabetic woman's chances of becoming pregnant, of having an uneventful pregnancy and delivering a normal child have been greatly increased by the use of insulin. The more nearly normal her metabolic processes can be made the more normal will be her course and the better the prognosis both for her health and that of the infant.

## CASE HISTORIES OF PREGNANT DIABETIC WOMEN TREATED AT THE CHICAGO LYING-IN HOSPITAL

CASE 1.—(47668) Patient, aged twenty-seven, para i, gravida ii. Normal pregnancy in 1925 with first symptoms of diabetes in 1926. Insulin requirement both before and during pregnancy varied greatly from time to time with a maximum dose of 70 units daily. Delivery at term of a 3,010 gm. female infant by cesarean section with accompanying sterilization Nov. 9, 1931. Complication: moderate hypertension. Mother and infant discharged in good condition.

CASE 2.—(59732) Patient, aged twenty-three, para i, gravida ii. Pregnancy in 1929 complicated by eclampsia with spontaneous delivery of thirty-seven weeks' fetus which died shortly after delivery. First symptoms of diabetes occurred six months later since which time she has been on a moderately restricted diet and an average of 50 units of insulin daily. Insulin requirement varied practically none during pregnancy. She was given a five-hour test of labor at term but since progress was not satisfactory she was delivered by cesarean section with accompanying sterilization on Aug. 26, 1932. Infant, male, 4,550 gm., normal. Complications: yeast infection, hydramnios, severe preeclamptic toxemia.

CASE 3.—(55029) Patient, aged thirty, para 0, gravida i. Onset of diabetes in 1927, controlled by diet and an average insulin intake of 30 units daily. When six months pregnant, insulin requirement was 90 units daily, at time of delivery 45 units. Delivered naturally June 30, 1932. Normal female infant, 4,015 gm. Mother and infant discharged in good condition.

CASE 4.—(65599) Patient, aged thirty-six, para iii, gravida iv. Pregnancies in 1917 with 3,800 gm. liveborn infant, 1926 with 5,800 gm. stillborn infant, 1930 with 4,500 gm. liveborn infant. Onset of diabetes in 1923. Disease controlled largely by diet with only occasional use of insulin. First seen Aug. 17, 1932, when four months pregnant. Impossible to control diabetes adequately because of lack of cooperation of patient. Delivered naturally of a 3,945 gm. macerated female infant on Feb. 19, 1933.

CASE 5.—(97804) Patient, aged thirty-six, para iv, gravida vi. Four normal liveborn infants; 1913, 2,700 gm.; 1916, 4,500 gm.; 1918, 3,600 gm.; 1922, 3,500 gm.; unintentional abortion at six weeks in 1933. First symptoms of diabetes in July, 1932, controlled by diet until July, 1933 when started taking 30 units of insulin; 65 units in January, 45 units in February, none by the end of March. Delivered naturally Apr. 18, 1934. Normal female infant, weight 4,000 gm. Insulin requirement 15 units daily following delivery until became pregnant again. At eight months required 60 units, at nine months 25 units, at time of delivery none. Delivered on Nov. 8, 1935, by cesarean section. Sterilized. Normal male infant, weight 4,685 gm. Complications of both pregnancies: syphilis, obesity, hypertension; of the second only, preeclampsia, yeast vaginitis.

CASE 6.—(106230) Patient, aged thirty-eight, para i, gravida vii. One normal delivery of 5,000 gm. liveborn infant in 1915 followed by 5 unintentional abortions. First seen June 14, 1934, when sugar was discovered in the urine. Sugar tolerance curve showed presence of diabetes mellitus. Blood sugar was controlled by diet of carbohydrate 110, protein 65, fat 100 without the use of insulin. Delivered naturally at term on Aug. 16, 1934, of a 3,610 gm. normal female infant. Complication: mild toxemia. Mother and infant discharged in good condition.

CASE 7.—(112772) Patient, aged twenty-two, para i, gravida ii. One normal delivery in 1931. First seen on admission to the hospital when six months pregnant Sept. 20, 1934, with history of continuous vomiting and absence of fetal movement for five days. Blood chemistry on admission was nonprotein nitrogen 107, chlorides 438, sugar 322, $CO_2$ combining power 25 volumes per cent. Diagnosis made of diabetic coma. Died undelivered twenty-four hours after admission. Had had no prenatal care and there had been no previous diagnosis of diabetes. Autopsy confirmed diagnosis.

CASE 8.—(99543) Patient, aged twenty-six, para 0, gravida ii, one unintentional abortion in 1930. Onset of diabetes in 1928; controlled by diet and an average of 10 units of insulin daily. Tolerance remained practically stationary during preg-

nancy. Medical induction followed by delivery at term (Dec. 3, 1934) by low forceps. Male infant, weight 3,470 gm. Complication: mild toxemia. Mother and infant discharged in good condition.

CASE 9.—(29871) Patient, aged thirty, para iii, gravida vi. Normal delivery in 1924 of 3,600 gm. infant, in 1926 of 3,150 gm. infant, in 1931 of 4,300 gm. infant; 2 unintentional abortions. Onset of diabetes in 1927, with dietary regime followed only moderately well since then; insulin requirement variable with maximum of 50 units. Delivered at thirty-eight weeks' gestation by cesarean section on Mar. 28, 1935. Sterilized. Infant normal, weight 3,925 gm.

CASE 10.—(125560) Patient, aged twenty-nine, para 0, gravida i. Glycosuria accidentally discovered in 1925, disappeared on slight modification of diet and did not reappear until Dec. 19, 1934, when patient was three months pregnant. Diet of protein 60, carbohydrate 150, fat 100 and 15 units of insulin was sufficient to prevent glycosuria. Delivered naturally Apr. 22, 1935, at thirty-one weeks' gestation. Infant died after two hours. Autopsy showed prematurity, slight hyperplasia of islands of Langerhans. Weight 1,820 gm.

CASE 11.—(74337) Patient, aged thirty-five, para i, gravida ii. Delivered one normal infant, date unknown. Onset of diabetes in 1932, controlled by diet and an average of 20 units of insulin. This was increased to 45 units by the thirty-second week of pregnancy, 70 units in the last four weeks, 60 units at term. Delivered by cesarean section Jan. 18, 1936. Sterilized. Normal female infant, weight 4,320 gm.

CASE 12.—(1312) Patient, aged thirty-four, para 0, gravida i. Under observation of medical department since onset of diabetes in 1932. Despite a strict diet the insulin ranged from 20 to 90 units. She became pregnant in November, 1935, and had such marked nausea and vomiting that acidosis developed. Because of the difficulty in controlling the diabetes in the presence of the complications of pregnancy a partial hysterectomy was performed Feb. 13, 1936. Discharged with diabetes well controlled.

CASE 13.—(146114) Patient, aged twenty-two, para 0, gravida i. Onset of symptoms during pregnancy. Placed on strict diet. Insulin required until last month of pregnancy. Delivered with aid of low forceps Apr. 18, 1936, of a normal male infant weighing 3,665 gm. Mother and infant discharged in good condition.

CASE 14.—(145185) Patient, aged seventeen, para 0, gravida i. No symptoms of diabetes; during pregnancy urine showed 1+ to 4+ sugar, during last two weeks sugar in urine glucose tolerance tests both before and after labor indicated true diabetes. Delivered with aid of low forceps August 13. Normal male infant, weight 3,330 gm. Mother and infant discharged in good condition.

CASE 15.—(158861) Patient, aged thirty-six, para iii, gravida iv. Three unintentional abortions at three to four months, 1932, 1933, 1934. First symptoms of diabetes in 1933; followed a diet and took approximately 35 units insulin daily for two years. During the last year has had no insulin, has not followed a diet and when urine has been tested was usually 4+. During last two months of pregnancy, when patient consulted clinic, urine was sugar-free on only mildly restricted diet. Patient admitted in first stage of labor, membranes having ruptured seventy-two hours before onset of labor. Fetal heart tones absent on admission. Delivered Sept. 1, 1936, by podalic version and extraction and embryotomy because of uterine inertia. Autopsy examination of the fetus failed to show any abnormality except an infiltration of polymorphonuclear leucocytes into the lung. Weight 3,510 gm.

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# A ROENTGENOGRAPHIC STUDY OF THE SUPERIOR STRAIT DURING PREGNANCY

## Preliminary Report

Donald J. Thorp, M.D., and Thomas Lough, A.M., R.T.,
Seattle, Wash.

*(From the Obstetrical and Radiological Departments, Swedish Hospital)*

FOR many years it has been recognized that relaxation of the pelvic joints occurs during pregnancy. The Hippocratic theory of "disjunctio pelvica" was, perhaps, the vanguard of this recognition. Throughout the ages this phenomenon was intermittently a pivot of controversy and, indeed, Francois Mauriceau in the seventeenth century refused to concede the point.

More recent years have brought out new substantiation of what was once only theory. Roentgenography as applied in obstetrics has played an important part in reactivating an interest in the mobility of the symphysis pubis and the sacroiliac articulations during pregnancy. It has been demonstrated that cyst formation, fissure formation, and hemorrhage into the joint cavities do occur in the articulations of the pelvis during pregnancy or labor. However, in a large series of obstetric patients, managed properly both antenatally and intranatally, one does not frequently observe symptoms and signs postpartum which are attributable to changes in the symphysis pubis or in the sacroiliac joints. The investigations of Lang and Haslhofer prove, however, that "changes in the sacroiliac joints must be considered occasionally as a cause of the backache so frequent in pregnant women and in those who have had many labors."

The predominant opinion holds that there is a widening of the pubic articulation and a concomitant separation of the sacroiliac articulations.

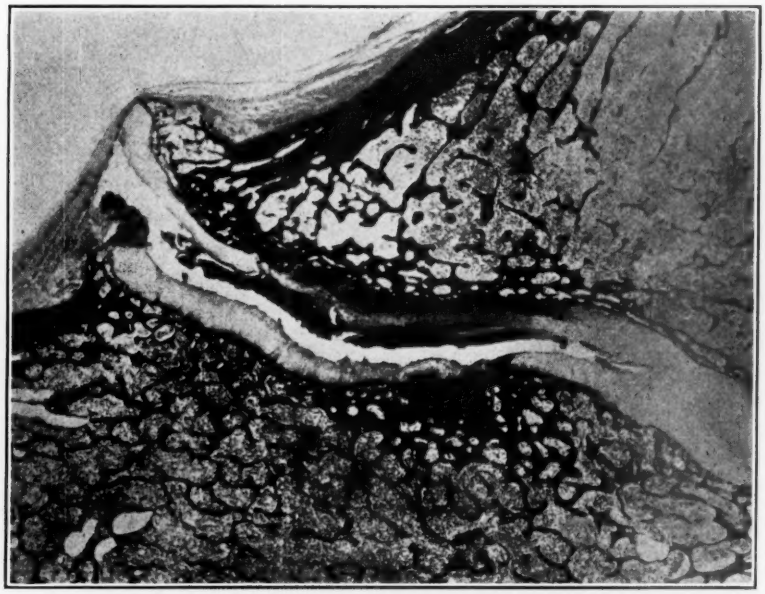

Fig. 1.—Articulatio sacroiliaca of a twenty-seven-year-old woman who had had 2 children. Note the formation of marginal exostoses at the terminal parts of this joint. Hemorrhage has occurred in the joint cavity. (From Lang, F. J. and Haslhofer, L.: Changes in Symphysis Pubis and the Sacro-iliac Articulations as a Result of Pregnancy and Childbirth. Arch. Surg. 25: 870, 1932. Courtesy of Archives of Surgery.)

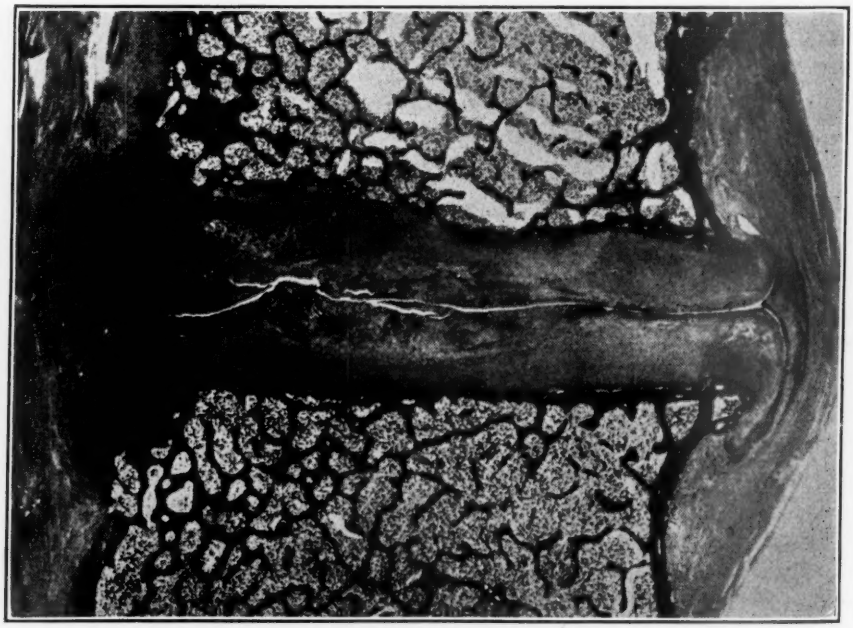

Fig. 2.—Symphysis pubis of a fifty-two-year-old woman who had had 3 children. The formation of a T-shaped cleft is seen. (From Lang, F. J. and Haslhofer, L.: see above. Courtesy of Archives of Surgery.)

Abramson, Sumner and Wilson state that the average increase in width of the symphysis during pregnancy is 7 or 8 mm. while the maximum is 12 mm. They believe the greatest increase at the symphysis occurs between the fifth and seventh months of pregnancy. Likewise these investigators conclude that no increase in the separation of the symphysis takes place during labor.

Reis, Baer, Arens, and Stewart were unable to demonstrate in 80 consecutive cases, by roentgen examination, any change in the pubic articulation during pregnancy, thus taking issue with Abramson, Sumner, and Wilson. They conclude that any increase in the span of the pelvic articulations takes place only during labor.

Hisaw has demonstrated the presence of a hormone in lower animals which, if injected into virgin guinea pigs, will produce relaxation of the pelvic ligaments. This is, according to Hisaw, a special fraction of the corpus luteum hormone which he named "relaxin." We may therefore conclude, as a basis for this study, that regardless of the time at which separation occurs it nevertheless does take place.

We have inquired as to whether or not this established widening of the joints occurs before labor starts and also whether or not it might favorably influence the outcome of labor especially in contracted pelves. Many an obstetrician has been impressed with the spontaneous delivery of a child through a superior strait which, in early pregnancy, proved by mensuration to be abnormally small. Many have recorded after the first examination and pelvimetry such notes as: "generally contracted pelvis; probable cesarean section," only to be surprised at the ease and rapidity with which the patient delivered.

Since there is relaxation of the symphysis pubis and the sacroiliac joints sometime antenatally, is it sufficient to enlarge the pelvic girdle enough to convert potentially difficult labors into easy ones?

We are able to answer this question at present only with respect to the possible changes which take place prior to the onset of labor. Subsequently we shall attempt to make similar determinations during labor.

This preliminary report is based upon measurement of the inlets of 25 women. No selection as to age, parity, or constitutional type was made. No study was undertaken, however, later than the sixteenth week of pregnancy. Our method is a modification of the Thoms technique of "applying roentgenometric methods of diagnosis to the problems of pelvimetry." While Thoms, Jarcho and others have established the most accurate method of taking simple pelvigrams, this study involves making two radiographic determinations on each patient: one early in pregnancy and another, under identical technical conditions, near term. Such a dual technique obviously opens the way for errors and both exposures on each individual patient must be identical in all conditions as is humanly possible.

## METHOD

Our technique consists first of permanent localization of landmarks in each patient. These points are the (1) central point of the superior margin of the

symphysis pubis and the (2) depression below the fifth lumbar vertebra, i.e., the upper angle of the Michaelis rhomboid. Thoms measures from "a point on the anterior surface about 1 cm. below the upper and anterior border of the symphysis." We have found by careful check upon the skeleton that the midpoint upon the

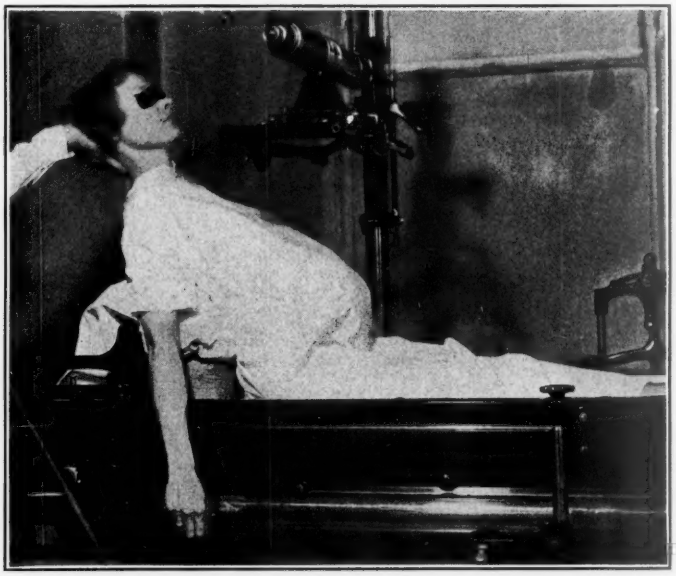

Fig. 3.—Patient in semisitting position, back arched forward by use of sandbag, thus bringing the plane of the inlet into the horizontal.

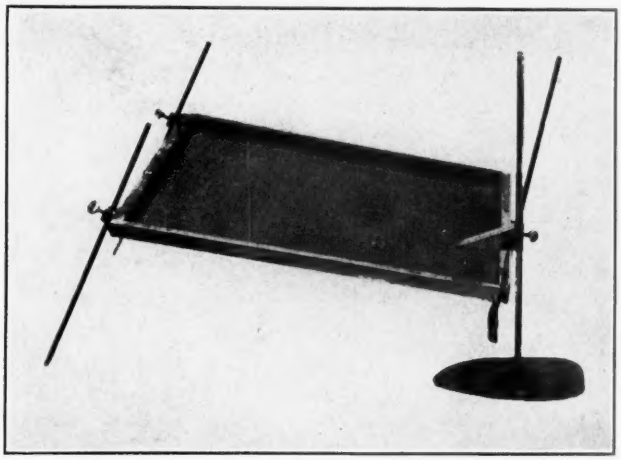

Fig. 4.—Centimeter lead grid on tripod with adjustable legs. Sliding vertical scale for measuring height of symphysis pubis.

superior border of the symphysis is well within constant accuracy for determining the true conjugate by x-ray. This has the advantage of easy identification at any time during pregnancy without danger of error in any given set of determinations.

Before, or at the time of, the first picture the depression below the fifth lumbar spinous process is located and a small wheal of India ink is injected intradermally.

With care, this may be done without disfigurement and has the advantage that months later the same landmark exists from which to measure when the second film is taken.

The patient is placed upon the table in a semirecumbent position with the lumbar spine arched forward in order to reduce the angulation which the plane of the

Fig. 5.—Sixteen weeks pregnant. Conjugate vera: 11.5 cm. Transverse conjugate: 12.5 cm.

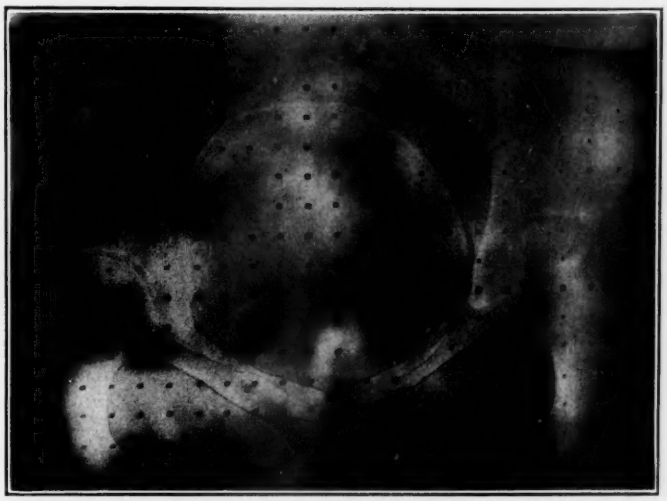

Fig. 6.—Same patient as in Fig. 5; thirty-nine weeks pregnant. Conjugate vera 11.25 cm. Transverse conjugate: 12.5 cm.

inlet makes with the plane of the table surface (Fig. 3). The method of determining distances from the symphysis and the posterior landmark is essentially that of Thoms and Jarcho. When the patient has been x-rayed and has been removed from the table, the centimeter lead grid is placed accurately in the same position occupied by the plane of the superior strait (Fig. 4). A flash exposure

is made as usual through this grid to imprint the dots upon the film making certain that the x-ray tube has not been moved since its adjustment for the radiograph of the patient.

Radiograph time of exposure varied with the patient. In the early pregnancy films two to three seconds was sufficient, but the films taken at term required four to six seconds' exposure due to the great thickness of soft tissue penetrated. All other technical factors remained the same with the entire series of patients.* The same person (D. J. T.) made all of the adjustments of the patients upon the x-ray table and made all of the measurements. This reduced human error to a minimum.

The only pelvic diameters commanding our attention in this study were the true conjugate and the transverse conjugate. We have not considered the bispinous diameter because the plane of the spines lies far enough below the plane of the inlet to admit error due to divergence of the x-rays. An approximation of this diameter, however, is of practical value where it is of serious consideration.

Figs. 5 and 6 show a typical pair of pelvigrams. The first film was taken at fifteen weeks of pregnancy. The second film was secured at the thirty-ninth week of gestation. In the earlier determination the conjugate vera and the transverse conjugate are 11.5 cm. and 12.5 cm., respectively, while in the second radiogram these dimensions are, respectively, 11.25 cm. and 12.5 cm. Thus, no enlargement in the area of the superior strait is demonstrated.

Table I presents actual measurements of the conjugate vera and of the transverse diameter in 10 of the 25 women. "A" represents the

TABLE I

| PATIENT | WEEKS OF GESTATION | DIMENSIONS | |
|---|---|---|---|
| | | CONJ. VERA | TRANS. DIAM. |
| 1 | A 12 | 12.0 cm. | 12.0 cm. |
| | B 36 | 12.5 | 13.0 |
| 2 | 8 | 12.0 | 11.8 |
| | 38 | 12.5 | 12.0 |
| 3 | 15.5 | 11.0 | 11.25 |
| | 38.5 | 11.25 | 10.75 |
| 4 | 14.0 | 12.0 | 14.5 |
| | 39.5 | 11.75 | 14.0 |
| 5 | 13 | 11.5 | 12.25 |
| | 39 | 12.0 | 12.5 |
| 6 | 14 | 13.0 | 14.5 |
| | 41 | 13.0 | 14.0 |
| 7 | 9 | 11.25 | 11.5 |
| | 41 | 12.0 | 11.75 |
| 8 | 16 | 12.5 | 13.0 |
| | 37 | 12.5 | 13.0 |
| 9 | 15.5 | 13.0 | 13.5 |
| | 38 | 13.75 | 13.5 |
| 10 | 10 | 13.25 | 13.0 |
| | 39.5 | 13.0 | 13.0 |
| AVERAGES TAKEN FROM 25 CASES | | 11.9 | 12.7 |
| | | 12.0 | 12.8 |

*All radiograms were made with General Electric x-ray equipment (KX No. 1); Potter-Bucky diaphragm at 30 inches distance; General Electric XP tube with 100 M. A. using 76 Kvp.

first radiogram taken and the gestation in weeks. "B" represents the second radiogram and the number of weeks of gestation.

One-half centimeter, plus or minus, may be accurately allowed for error in technic. This is according to Thoms' experience, and we also have found the same latitude permissible in radiographic experiments upon the skeleton. This explains the apparent "shrinking" of an occasional dimension in the later films. Furthermore, none of the numerical increases in the dimensions of the inlet at term can be considered actual increases. Certainly one cannot conclude that there is an increase of the dimensions of the superior strait during pregnancy which will facilitate an otherwise slow and difficult labor. There is no expansion of the area of the inlet prior to the onset of labor.

Attention is directed in Fig. 7 to the fallacy of taking x-rays with the patient in the supine or prone positions to secure information

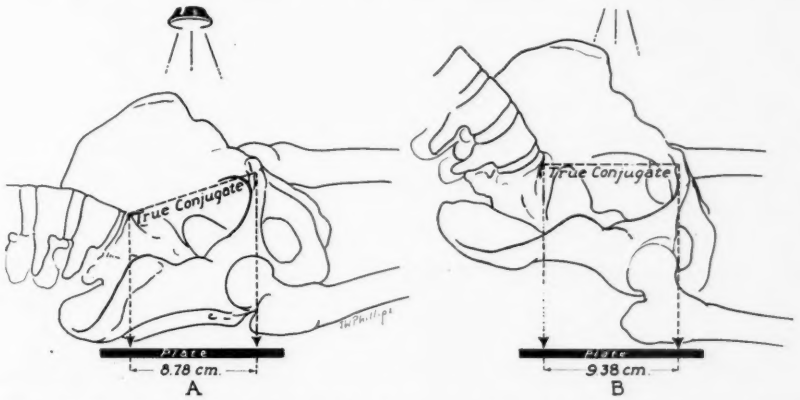


Fig. 7.—True conjugate on skeleton drawn to scale. *A* shows erroneous figures (8.78 cm.) with patient in prone position. *B* shows actual figures (9.38 cm.) when inlet is parallel to table.

upon the size of the inlet. These two figures were drawn exactly to scale. The values inscribed are the actual measurements of the true conjugate on a skeleton. Note the orthographic projection of this dimension in Fig. 7-*A* when the subject is supine, and the shortening of the projected delineation upon the radiographic film. Fig. 7-*B* represents a true dimensional projection of the conjugate vera upon the film and reveals an increase of 0.6 cm. over the fallacious value in Fig. 7-*A*.

## CONCLUSIONS

1. There has been for many years a supposition that throughout pregnancy an enlargement of the pelvic inlet occurs.

2. Relaxation of the so-called pelvic joints during pregnancy is definitely established but such relaxation is of no apparent value in cases of dystocia involving the superior strait.

3. Radiographic studies of exactitude reveal no definite and reliable increase in the capacity of the pelvic inlet or superior strait.

4. Erroneous conclusions may be drawn concerning cephalopelvic proportion or disproportion from radiograms of the superior strait taken with the subject in the supine or prone positions.

5. The possibility of an increase in the dimensions and capacity of the superior strait during actual labor is to be studied subsequent to this report.

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MEDICAL-DENTAL BUILDING

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# DIABETIC OR MYCOTIC VULVOVAGINITIS

## SUPPLEMENTARY REPORT

H. CLOSE HESSELTINE, M.D., AND L. K. CAMPBELL, M.D.,
CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, The University of Chicago, and the Department of Medicine, Rush Medical College)*

IN 1933 a preliminary report[1] from a study of 21 diabetic (diabetes mellitus) patients with "diabetic vulvitis" indicated that fungi were the etiologic agents. At that time only impressions were given as the number of patients was too small to draw conclusions, but since then an additional 37 patients with "diabetic vulvitis" have been studied. This gives in all 58 diabetic patients with vulvitis and pruritus. Simultaneously 53 diabetic females without vulvitis and/or pruritus and 38 "control" individuals were observed, cultured, and tested. Thus the grand total is 149, of which 111 were diabetic patients; of the 111 patients 97 were adults and 14 preadolescents. The results not only confirm the original impressions but show most convincingly that the etiologic agent of "diabetic vulvitis" is usually, if not always, a fungus. Furthermore, a slight correction will be made regarding the particular type of fungi responsible for this inflammatory process.

Until 1931, when Plass, Hesseltine, and Borts[2] pointed out that diabetes is a predisposing factor for such infections, the modern American gynecologic textbooks and other publications had not indicated that fungi were etiologic agents of "diabetic vulvitis." Foreign literature was of the same tenor. On the other hand, vulvovaginal mycoses were recognized by Mayer,[3] von Winckel,[4] Haussmann,[5] and

others in the latter part of the nineteenth century, and many of the modern textbooks of gynecology[6-14] give brief reference to the infrequency and mildness but do not correlate predisposing and precipitating factors. Le Blaye,[15] Davis,[16] Popoff, Ford, and Cadmus,[17] Odland and Hoffstadt,[18] and others report in the recent literature that the disease is not common and is generally mild. The reports of Wong and Kurotchkin,[19] Karnaky,[20] Hesseltine,[1] Woodruff and Hesseltine,[21] Plass and coworkers,[2] and others indicate a frequent incidence. They point out the possibility of severe irritation in a few patients while some have little distress and others may even be symptomless carriers.

The relation of vulvovaginal mycoses caused by the yeastlike fungus to available glucose has not been sufficiently stressed. In diabetes the frequent spill of glucose over the vulva would produce a more favorable environment even if there was not an appreciable alteration in the cellular carbohydrate content. In pregnancy a similar environment might result from the unusual accumulation (normally) of the glycogen-like substances in the vaginal epithelium, which in turn is converted into utilizable (carbohydrate) materials as the epithelium is cast off and broken down.

The name "diabetic vulvitis" was given because of the rather characteristic clinical entity observed not infrequently in diabetic females, because the onset or exacerbation was so often related to an increase in glycosuria, and because clinical improvement often occurred after control of the diabetes. Such reasoning did not explain the occasional persistent vulvitis following proper diabetic management or the clinical improvement produced by certain antiseptics (fungicides) before the institution of diabetic management. For many years it was taught that the reaction was brought about by the glucose or irritating substances in the urine, and many texts still so state.

If "diabetic vulvitis" is a mycosis one should (a) be able to secure positive fungous cultures, (b) fail to reproduce the symptoms or tissue change by applying the various substances in the diabetic urine to the vulva in the absence of fungi, and (c) show that vulval mycosis presents the same clinical features. The tables and explanations fulfill conditions of (a) and (c) and part of those of (b).

Plass and coworkers,[2] and Hesseltine[1] have described the following vaginal and vulval changes due to yeastlike fungi. The vulva is slightly swollen, tender, with a reddish blue under-color and a thin, grayish surface. The epithelium appears definitely injured. Abrasion or excoriation may have resulted from scratching. There is an increase of local heat subjectively, and the area is warm to touch. The area most often involved extends from the hymenal ring, or slightly above in some instances, outward. It usually remains limited to the moist surfaces but in the severe cases it extends upward to the mons veneris, outward to the crural fold, and posteriorly to encircle the anus. The labia minora with the prepuce show the greatest reaction usually. Some small whitish areas (thrush spots) or caseous material may be observed. If the surface epithelium is rubbed or scraped the superficial portion of the epithelium may be lost over small areas leaving a reddened but nonbleeding

base. One may gather the impression that the vulva appears "cooked" or "boiled." The appearance of the vulval mycosis may resemble closely an early chronic atrophic dermatitis of the vulva (kraurosis) as has been illustrated by Adair and Davis.[22] In atypical cases the surface may appear to be acutely inflamed, while in some mild cases very little reaction takes place. In the chronic cases hypertrophy of the epithelium and even pigmentation may occur. The not uncommon secondary bacterial invasion may produce a chronic dermatitis. Thus the appearance of "diabetic vulvitis" and mycotic vulvitis are identical.

The symptoms of "diabetic vulvitis"[6-12] and mycotic vulvitis[1, 2, 17, 20] are also alike. The only constant symptom is pruritus. Other symptoms of tenderness, pain, discharge, heat, etc., are variable and not necessarily related to the severity of the reaction. Some patients report that the pruritus may be so compelling that scratching is avoided only with difficulty. Patients may awaken themselves from deep sleep to find that the vulval epithelium has been broken and injured by extensive scratching. No vulval itching can be more severe, chronic atrophic dermatitis not excepted. Fortunately most patients with mycotic vulvitis do not have such severe symptoms.

Originally the diagnosis of "diabetic vulvitis" was made by observing this characteristic vulvitis in a diabetic patient. Usually these patients had a moderately severe glycosuria, but even in the absence of "glucose spill" it has been assumed that there might be some causative irritating substances (other than glucose). The clinical diagnosis of a vulval mycosis is made by the characteristic appearance alike in diabetic and nondiabetic patients. There may be a vaginal mycosis with thrush patches or caseous material along with the vulvitis. The diagnosis of either is easily verified by finding fungi in direct smears or on cultures of Sabouraud's media (Plass and others).[2] Incubation at 37° C. for twenty-four to forty-eight hours is usually sufficient time. The fungi grow by the formation of spherical or oval buds or conidia and in some instances by mycelia. These units are very distinctly gram-positive. The buds are about as large as white cells but are easily distinguished. The mycelia are long, heavy structures. The junctions present somewhat the appearance of the joints of a bamboo stalk. The mycelia may branch and conidia grow at the junction or terminal portion.

In the study of these 111 diabetic patients (Chart 1) and 38 control individuals, cultures were made routinely on Sabouraud's medium. Ordinarily, only single but well-planted cultures were obtained from each patient. One might suggest that such routine would fail to give a large incidence, especially in the control series, but it has been learned from experience that the error is only slight in the hands of one accustomed to this type of investigation.

It has been demonstrated by Plass and others[2] that yeastlike fungi may be recovered from the vulva and vagina of apparently normal adults, yet Hesseltine and others[23] have shown that these same organisms, although pathogenic for some, are not disease-producing in all instances.

The 111 patients are made up of two groups: 58 with vulvitis and 53 without vulvitis. In the group of 58, 55 had positive fungous cultures. The 3 negative ones will be explained in the discussion of Table II. There was only one preadolescent patient in this group. The group of 53 had 13 preadolescent patients. Four adults and one child had positive cultures. These five patients were all without symptoms and had previously been free from vulvitis or irritation.

Table I was devised to show the general morphologic method of identifying the yeast and yeastlike fungi isolated from the human vagina and vulva. In the previous report it was stated that endomyces were

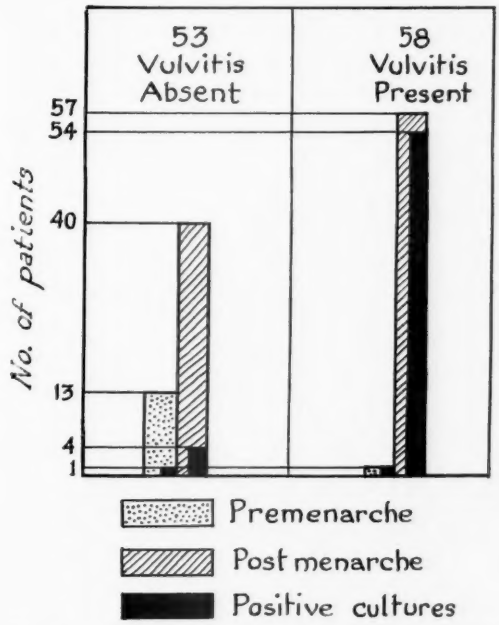


Chart 1.—Incidence of fungi in diabetic females.

recognized. These actually were monilia since vacuoles, or bodies, had been mistaken for endospores in the early study. Repeated fermentation tests and morphologic examinations now definitely confirm the correctness of this last statement for all the strains available from the University of Chicago series. Hopkins and Hesseltine,[24, 25] using their methods, found only monilia and cryptococci. The monilia definitely predominated. Saccharomyces was not found although it has been isolated from the human vagina by other workers. Endomyces is an unproved pathogen for the genital tract and so far has not even been isolated from this site. Hopkins and Hesseltine,[24, 25] in special studies of 81 strains of cryptococci and monilia isolated from oral thrush and vulvovaginal mycoses, proved that Types 1 and 2 of cryptococci and

*Monilia albicans* and *Monilia candida* (Types 2 and 3 of Stovall and Bubolz) with a few atypical strains are the usual fungi present in the vagina.

Because many diabetic females are free from vulvitis it required a few years of cooperation with internists and pediatricians to secure a group of 58 with vulvitis. It will be noted in Table II that prior to 1931 the material was from the University of Iowa while after July 1, 1931 the patients were from either Rush Medical College or the University of Chicago Clinics. Of the 111 the University of Iowa supplied 42, but of this number only 7 had vulvitis and 14 were preadolescent patients. One of the preadolescents had vulvitis, which leaves 22 adults for the control series. At Chicago no premenacmic patients were studied. At Rush 19 cases with and 9 without vulvitis were collected, while from the University of Chicago Clinics 32 with and 9 without vulvitis were cultured. The sexually immature, mature, and postmature groups show little variation.

TABLE I. MORPHOLOGIC COMPARISON OF YEASTLIKE FUNGI ISOLATED FROM DIABETIC PATIENTS WITH VULVITIS TO SACCHAROMYCES (YEASTS) AND ENDOMYCES

| | CRYPTOCOCCI | MONILIA | SACCHAROMYCES | ENDOMYCES |
|---|---|---|---|---|
| Conidia | Round or oval | Round or oval | Round or oval | Round or oval |
| Mycelia | None | Branched and jointed | None or rudimentary | Branching and jointed |
| Endospores | None | None | True—2 to 4 usual | True—2 to 4 usual |

The 58 patients with vulvitis (Table III) ranged in age from twelve to seventy-three years. The patient of undetermined age was one in mid-adult life. It will be obvious at a glance that a large number of the patients (exactly 36) were in the postmenopausal period, while only 1 was premenacmic and 21 were menacmic. A relationship of parity or nulliparity to the vulvitis is not obvious. All were nonpregnant patients but one, aged thirty-seven years, whose first gestation was of twenty weeks' duration. The term "menacme" means in the period from menarche to the menopause, while "premenacme" and "postmenacme" designate before and after menacme respectively. There were three of the entire group who had negative fungous cultures. These were aged fifty, fifty-four, and undetermined. The first two had applied antiseptics to the vulva only a few hours before coming to the clinic. The interference in the third patient was menstrual flow contaminating the entire vulva. Unfortunately these patients did not present themselves at the clinic again when the observer and culture material were available.

The age incidence is comparable in diabetic and control groups. The data on childbearing have been confused, but deviation in either direction appears to be of little significance.

TABLE II.* INSTITUTIONAL SOURCES, SERVICE ASSIGNMENT, AND MENACMIC AGE OF DIABETIC PATIENTS WITH AND WITHOUT VAGINITIS

| COURTESY OF | | VULVITIS | | | | NO VULVITIS | | | TOTALS |
|---|---|---|---|---|---|---|---|---|---|
| | | PRE. | MEN. | POST. | UND. | PRE. | MEN. | POST. | |
| University of Iowa† College of Medicine Medical Department 1930-31 | Drs. F. M. Smith and C. W. Baldridge | 0 | 3 | 3 | 0 | 0 | 12 | 10 | 28 |
| Pediatrical Department† 1930-31 | Dr. P. C. Jeans | 1 | 0 | 0 | 0 | 13 | 0 | 0 | 14 |
| | | 7 | | | | 35 | | | 42 |
| University of Chicago Div. Biol. Science Medical Department 1931-36 | Drs. Louis Leiter H. L. Schmitz Allan Kenyon Henry T. Ricketts | 0 | 12 | 19 | 1 | 0 | 5 | 4 | 41 |
| Rush Medical College Medical Department 1931-33 | Drs. R. T. Woodyatt L. K. Campbell | 0 | 4 | 14 | 1 | 0 | 4 | 5 | 28 |
| | | 51 | | | | 18 | | | 69 |
| Totals | | 1 | 19 | 36 | 2 | 13 | 21 | 19 | 111 |
| | | 58 | | | | 53 | | | |

*Pre., Premenacme or before menarche; Men., menacme or menarche to menopause; Post., postmenacme or after menopause; Und., undetermined.

†Taken from data of Plass, Hesseltine and Borts.

TABLE III.* DIABETIC PATIENTS WITH VULVITIS

| AGE | NUMBER | MATURITY | PAROUS | FUNGOUS CULTURE | REMARKS |
|---|---|---|---|---|---|
| 12 | 1 | Men. | No | + | |
| 13 | 1 | Pre. | No | + | |
| 14 | 1 | Men. | No | + | |
| 16 | 2 | Men. | No | + | |
| 24 | 1 | Men. | Yes | + | |
| 28 | 1 | Men. | No | + | |
| 31 | 1 | Men. | Yes | + | |
| 33 | 1 | Men. | Yes | + | |
| 34 | 1 | Men. | Yes | + | |
| 35 | 1 | Men. | Yes | + | |
| 37 | 1 | Men. | No | + | First pregnancy—5 months |
| 38 | 1 | Men. | Yes | + | |
| 39 | 2 | Men. | Yes | + | |
| 41 | 2 | Men. | Yes | + | |
| 45 | 4 | 1 Und.<br>3 Post. | Yes | + | |
| 47 | 1 | Post. | Yes | + | |
| 48 | 5 | 3 Men.<br>2 Post. | Yes | + | |
| 49 | 1 | Post. | Yes | + | |
| 50 | 2 | Post. | 1 Und.<br>1 Yes. | +<br>- | <br>Antiseptic on vulva |
| 51 | 1 | Post. | Yes | + | |
| 53 | 2 | Post. | 1 Und.<br>1 Yes. | +<br>+ | |
| 54 | 1 | Post. | Yes | - | Antiseptic on vulva |
| 56 | 3 | Post. | 1 Und.<br>2 Yes. | +<br>+ | |
| 57 | 3 | Post. | 1 No<br>2 Yes. | +<br>+ | |
| 59 | 2 | Post. | Yes | + | |
| 60 | 1 | Post. | Und. | + | |
| 61 | 2 | Post. | Yes | + | |
| 63 | 1 | Post. | Und. | + | |
| 64 | 2 | Post. | Yes | + | |
| 65 | 3 | Post. | Yes | + | |
| 66 | 2 | Post. | Yes | + | |
| 69 | 2 | Post. | 1 Und.<br>1 Yes. | +<br>+ | |
| 72 | 1 | Post. | Und. | + | |
| 73 | 1 | Post. | Yes. | + | |
| Undet. | 1 | Und. | Und. | - | Menstruating |

*Pre., Premenacme or prior to menstruation; Men., menacme or menarche to menopause; Post., postmenacme or after menopause; Und., undetermined.

A larger number of diabetic females could have been procured through the courtesy of the medical staffs, but 53 (Table IV) seemed adequate for general purposes when such great differences in the incidence of fungi existed. The total of 53 is made up by 13 premenacmic, 20 menacmic, and 20 postmenacmic patients, all entirely free from vulvitis clinically and symptomatically. It is also interesting to note that one of the 13 immature females, 3 of the women of reproductive age and one of the postmenstrual group had positive cultures for yeast. Those in this control series with positive cultures must be classified as carriers according to the reports of Plass and others,[2] Woodruff and Hesseltine,[21] and others. Nineteen of those with negative cultures did admit, when in-

TABLE IV.* DIABETIC PATIENTS WITHOUT VULVITIS

| AGE | NUMBER | MATURITY | PAROUS | FUNGOUS CULTURES | REMARKS |
|---|---|---|---|---|---|
| Und. child | 1 | Pre. | No | – | |
| 6 | 2 | Pre. | No | – | |
| 7 | 2 | Pre. | No | – | |
| 9 | 1 | Pre. | No | – | |
| 10 | 1 | Pre. | No | – | |
| 11 | 1 | Pre. | No | – | |
| 12 | 4 | 3 Pre. | No | 1+<br>2– | Carrier |
| | | 1 Men. | No | – | |
| 14 | 4 | 1 Pre. | No | – | |
| | | 3 Men. | No | – | |
| 15 | 1 | Pre. | No | – | |
| | 1 | Men. | No | – | |
| 16 | 1 | Men. | No | + | Carrier |
| 17 | 2 | Men. | No | – | |
| 20 | 1 | Men. | No | + | Carrier |
| 21 | 1 | Men. | No | – | |
| 26 | 1 | Men. | No | – | Five months pregnant |
| 29 | 1 | Men. | No | + | Carrier |
| 39 | 1 | Men. | Und. | – | |
| 41 | 1 | Men. | Yes | – | |
| 42 | 1 | Men. | Yes | – | |
| 43 | 1 | Men. | Yes | – | |
| 44 | 1 | Men. | Und. | – | |
| 45 | 2 | Men. | Yes | – | |
| 48 | 1 | Post. | No | – | |
| 49 | 2 | Post. | Yes | – | |
| 50 | 2 | 1 Men. | Yes | – | |
| | | 1 Post. | Yes | – | |
| 52 | 1 | Post. | Yes | – | |
| 53 | 1 | Post. | Yes | – | |
| 56 | 1 | Post. | Yes | – | |
| 58 | 2 | Post. | Yes | – | |
| 60 | 3 | Post. | Yes | – | |
| 61 | 1 | Post. | Yes | – | |
| 64 | 1 | Post. | Yes | – | |
| 65 | 4 | Post. | Yes | – | |
| 70 | 1 | Post. | Yes | + | Carrier |
| 72 | 1 | Post. | Yes | – | |

*Pre., Premenacme or prior to menstruation; Men., menacme or menarche to menopause; Post., postmenacme or after menopause; Und., undetermined.

terrogated directly, that they had had vulva irritation at some time previously. Since there are various causes for such complaints and since this complaint was not directly related in all instances to glycosuria, further comments are unnecessary. The age incidence appears unimportant and speaks for itself.

Because particular attention may be focused upon the children (premenacme) Table V was prepared from the previous data. Out of 14 consecutive diabetic patients admitted to the pediatric service (Courtesy of Dr. P. C. Jeans, head of the Children's Hospital in Iowa City) only one admitted vulval irritation, and this was one of two with positive yeast cultures. The vulval appearance conformed to that of a mild mycosis and no other etiologic agent could be found. The other case with positive yeast culture must be classified as a carrier. Not one of

the 14 had menstruated although several, including those with positive cultures, showed definite evidence of entering or approaching the adolescent stage. Thus, there was one mycotic vulvitis, one fungous carrier,

TABLE V. PREMENACMIC PATIENTS

| AGE | NUMBER | FUNGOUS CULTURES | VULVITIS |
|---|---|---|---|
| Undetermined | 1 | Negative | No |
| 6 | 2 | Negative | No |
| 7 | 2 | Negative | No |
| 9 | 1 | Negative | No |
| 10 | 1 | Negative | No |
| 11 | 1 | Negative | No |
| 12 | 3 | 2 Negative | No |
| | | 1 Positive | |
| 13 | 1 | Positive | Yes |
| 14 | 1 | Negative | No |
| 15 | 1 | Negative | No |
| Totals | 14 | | 1 Vulvitis |
| | | 2 Positive | 1 Carrier—no vulvitis |
| | | 12 Negative | 12 No vulvitis |

All from Dept. of Pediatrics—Children's Hospital, Iowa City, University of Iowa, Courtesy of Dr. P. C. Jeans

TABLE VI. REACTION OF 13 PATIENTS TO GLUCOSE (10 PER CENT) VULVAL DOUCHES (SUBSTITUTE GLYCOSURIA)

| AGE | MONTHS PREGNANT | COMPLICATIONS | DAYS OF WASH | TISSUE CHANGE OR SYMPTOMS |
|---|---|---|---|---|
| | | *Fungi Absent* | | |
| 20 | 0 | Salpingitis | 14 | None |
| 22 | 6 | Pulmonary tuberculosis | 11 | None |
| 22 | 5 | Threatened premature labor | 5 | None |
| 24 | 8 | Coarctation aorta | 3 | None |
| 28 | 8 | Hypertension | 10 | None |
| 28 | 6 | Hypertension | 10 | None |
| 30 | 6 | Pulmonary tuberculosis | 22 | None |
| 38 | 7 | Nephritis | 11 | None |
| 40 | 8 | Habitual abortions | 10 | None |
| | | *Fungi Present* | | |
| 20 | 8 | Cardiac, fungous carrier | 5 | Sl. injection |
| 24 | 5 | Pulmonary tuberculosis, vaginal mycosis | 1 | Acute exacerbation |
| 29 | 7 | Threatened premature labor, fungous carrier | 1 | Severe |
| 37 | 8 | Diabetic, vaginal mycosis | 4 | Marked |

REACTION OF 25 PATIENTS TO GLUCOSE (95 PER CENT) OR LACTOSE (95 PER CENT) WITH CITRIC ACID (5 PER CENT) VAGINAL INSUFFLATIONS*

| | FUNGI ABSENT | | | FUNGI PRESENT | | |
|---|---|---|---|---|---|---|
| | NO. | PATIENTS | TISSUE CHANGES OR SYMPTOMS | NO. | PATIENTS | TISSUE CHANGES OR SYMPTOMS |
| Glucose and citric acid | 4 | Nonpregnant | None | 5 | Pregnant | Mycosis produced or made worse |
| Lactose and citric acid | 4 | Nonpregnant | None | 12 | Pregnant | None |
| | 8 | | | 17 | | |

*After Adair and Hesseltine: AM. J. OBST. & GYNEC. 32: 1, 1936.

and 12 without evidence of a vulvitis past or present, as elicited from the patient, the patient's parents, or the referring physician.

The data in Table VI support the previous experimental findings that glucose as such in either aqueous solution or powder is nonirritating. The first portion of the table gives data for those patients without fungi who had 250 c.c. of a 10 per cent aqueous solution of glucose poured over the vulva 5 times daily. The shortest period of exposure was three days in one, and ten or more days in 7. The longest continuous treatment extended to twenty-two days. Perhaps these periods are too short, but when the same glucose solution was poured over the vulva of patients with fungi present, symptoms and findings typical of a mycosis appeared in one to five days. Thus, one must admit that the fungi have some direct relation to the vulvitis. The gestational state and diagnosis are indicated for each patient. According to Hawk and Bergeim[26] the urine of diabetic mellitus patients seldom, if ever, reaches 10 per cent glucose concentration or contains over 125 gm. of glucose in twenty-four hours. Thus with 1,250 c.c. used during each twenty-four hours the total of 125 gm. of glucose was washed over the vulva in the control cases without producing or inducing any reaction. Yet when fungi were present the reaction occurred promptly.

The last portion of Table VI was taken from the report of Adair and Hesseltine[27] on the treatment of vaginal trichomoniasis. The mixture of glucose and citric acid or lactose and citric acid was 95 per cent to 5 per cent, respectively. More recently these sugars, especially lactose, have been used without citric acid and the same responses continue. Karnaky[28] reports that glucose induces a mycosis when monilia are present unless some fungicide is added to prevent it. In those cases with fungi present the citric acid did not prevent the exacerbation of the disease by glucose although lactose appeared innocuous.

## DISCUSSION

In addition to the data given in two or three instances all vulval irritation was relieved at least partly by using fungicidal therapy before the patient was placed under diabetic management. There have been a few diabetic patients whose vulvitis did not improve with proper diabetic management and the disappearances of the glycosuria, but cures were prompt with fungicidal therapy.

Infrequently one may observe, as was done in this series, instances of the spouse being either the recipient or the disseminator of the fungi. Males appear to be less susceptible than females. The reports of the urologists show that all instances of balanitis occurred in uncircumcised patients.

The source of these yeastlike fungi is probably multiple, but is most likely the hands, clothes, sexual partners, and feces.

At the Chicago Lying-In Hospital and the University of Chicago Clinics (Max Epstein) diabetes mellitus has been diagnosed in 4 of 32 patients with vulvitis. Consequently, one should suspect all nonpregnant patients with mycotic vulvitis as being diabetics until definite evidence to the contrary is available.

## CONCLUSIONS

1. In the presence of monilia or cryptococci the application of glucose in powder or aqueous solution will be associated usually, if not always, with the development of a vulvovaginal mycosis or will cause exacerbations of mycosis.

2. In the absence of yeastlike fungi the application of glucose in powder or aqueous solution has produced no symptoms or tissue changes.

3. The incidence of fungi in diabetes mellitus patients with vulvitis, and the similarity of the clinical appearance of mycotic vulvitis and of "diabetic vulvitis" justifies the previous statement that "diabetic vulvovaginitis is an infection, usually a mycosis, and rarely, if ever, an irritation from products in the urine."

4. Glucose available in the urine or the tissues favors the development of a vulval mycosis, just as its topical application may do.

5. Fungicidal therapy will cure "diabetic vulvitis."

6. Vulval mycosis occurred in diabetic patients from twelve to seventy-three years of age.

7. Whenever mycotic vulvitis is found in a nonpregnant patient one should exclude the possibility of diabetes mellitus.

8. Either "mycotic vulvitis" or "fungous vulvitis" is correct and accurate and should replace the incorrect, misleading and obsolete term "diabetic vulvitis."

9. Even such terms as "aphthous vulvitis," "thrush vulvitis," or "yeast vulvitis," do not conform to the modern taxonomy.

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# ON CERTAIN RELATIONSHIPS OF CALCIUM IN THE BLOOD SERUM TO CALCIUM BALANCE AND BASAL METABOLISM DURING PREGNANCY*

S. Idell Pyle, M.S., Martha Potgieter, Ph.B., and George Comstock, B.S., Yellow Springs, Ohio

THE effects of normal pregnancy upon the level of serum calcium and the relation between various forms of calcium ingestion and calcium in the serum have been studied extensively both on the human and on laboratory animals. Few studies are available where the degree of relationship between all the elements of the alimentary balance, serum calcium and basal metabolism have been studied simultaneously during pregnancy and these data therefore are presented to add to information already available about such relationships.

A three-day test period for sampling mineral balances during pregnancy has been studied at Fels Research Institute for the past four years. The findings have been compared with mineral metabolism data collected by using other types of test periods,[1] and the results to date seem to show that some interpretation can be made of trends of mineral and nitrogen metabolism when this method of sampling is used within the limits between which the ingestion of our subjects varied. The subjects of the experiment were shown how to weigh their food and were instructed to eat the same kind and quantity for each of three successive days. On the third day the food was sampled and collections of the twenty-four hour excretion of urine and the feces from the corresponding twenty-four-hour ingestion were made. On the morning of the fourth day blood was drawn for serum calcium immediately after the basal metabolic rate was determined.

Serum calcium was determined by the method of Folin and Wu, balance calcium by permanganate titration after dry ashing all samples, phosphorus on the ashed sample by the method of Embden and Fetter,

*The work was done at the Samuel S. Fels Research Institute as part of a series of studies on metabolism during pregnancy. The writers wish to express their appreciation to Elton Huff and Virginia Torbet for some of the analyses included in the study and to Dr. L. W. Sontag, Director, for his active interest in the work.

chlorides by the method of Volhard and Harvey, and basal metabolism by the Dubois method in duplicate. The raw data are given in Table I.

Serum calcium-calcium balance relations could be studied in various ways. We have used here Pearson's standard correlation technique. Each constituent included in the balance—food, feces, and urine—was related in turn to the serum calcium, the weight gain of the mother, and her oxygen consumption.

The usual method of expressing balance is in net. This method obscures some aspects of the distribution of calcium which seemed pertinent to the question we were studying. Hence, we used a series of ratios in addition to net to see if the movement of calcium through the blood stream and channels of excretion could be studied more clearly from them than from the net. Fraction I, therefore, is serum calcium minus urinary calcium each expressed in milligrams per cubic centimeter. Fraction II is food calcium ingested during the twenty-four hours minus the corresponding fecal calcium, and Fraction III is twenty-four-hour calcium ingestion minus the twenty-four-hour excretion of calcium in the urine.

Basal metabolic rate figures as such of course depend upon the weight, height, and age of the subject. Hence we used the average oxygen consumption per minute during the standard basal test period in these comparisons. This is discussed as *oxygen consumption.* The effects of weight changes upon the net and serum calcium and the oxygen consumption were studied either in relation to weight on the test day or weight gain up to that stage in pregnancy. Urinary phosphorus and chlorine and certain elements of the calcium balance, the serum calcium and basal metabolism were interrelated also.

In making interpretations we arbitrarily grouped the correlations into three categories regardless of the sign of the r. Correlations ranging between 0 and plus or minus 0.3 were said to show that the specific items compared were *independent;* if the r was plus or minus 0.3 to 0.6 inclusive the items were said to be *somewhat* related, and a correlation of plus or minus 0.6 and above is considered here to indicate a *fair degree* of relationship.

*Serum Calcium.*—Serum calcium was independent of and therefore not definitely affected by the calcium ingested during these tests. The types and levels of ingestion chosen by the women had varied within the range generally accepted as fairly adequate in quantity. The oxygen consumption and weight or gain in weight had as little relation to it; the same status existed between serum calcium and Fraction III, and either the urinary calcium or phosphorus.

| | r | $P.E._r$ |
|---|---|---|
| Serum calcium and calcium ingestion | = -0.16 | ± 0.09 |
| Serum calcium and weight | = -0.03 | ± 0.12 |
| Serum calcium and weight gain | = -0.18 | ± 0.08 |
| Serum calcium and Fraction III | = -0.15 | ± 0.09 |
| Serum calcium and urinary calcium Mg./c.c. | = -0.24 | ± 0.11 |
| Serum calcium and urinary phosphorus Mg./c.c. | = -0.08 | ± 0.11 |

TABLE I. CALCIUM BALANCES, SERUM CALCIUM, OXYGEN CONSUMPTION AND WEIGHT GAIN DURING PREGNANCY

| SUBJECT, AGE, NORMAL WT. | DAYS PREDELIVERY | SERUM Ca, MG. PER C.C. | URINARY Ca, MG. PER C.C. | FECAL Ca, MG. PER C.C. | FOOD Ca, GRAMS PER DAY | Ca BAL. GRAMS PER DAY | OXYGEN CONSUMPTION | WEIGHT GAIN, POUNDS | URINARY P, MG. PER C.C. | URINARY CHLORIDES, MG. PER C.C. |
|---|---|---|---|---|---|---|---|---|---|---|
| IIIa | 165 | 0.099 | 0.120 | 1.21 | 1.06 | −0.38 | 190 | 2.0 | 0.542 | ---- |
| 26 yr. | 135 | 0.099 | 0.096 | 1.70 | 1.90 | +0.02 | 196 | 6.5 | 0.525 | ---- |
| 138 lb. | 109 | 0.116 | 0.088 | 1.75 | 1.82 | −0.07 | 193 | 13.0 | 0.644 | ---- |
| | 79 | 0.115 | 0.194 | 1.39 | 1.14 | −0.54 | 206 | 16.5 | 0.511 | ---- |
| | 51 | 0.113 | 0.200 | 1.15 | 1.55 | +0.14 | 218 | 22.0 | 0.656 | 2.92 |
| | 23 | 0.126 | 0.091 | 1.10 | 1.96 | +0.68 | 230 | 25.3 | 0.406 | 2.87 |
| IIIb | 196 | 0.100 | 0.194 | 1.90 | 2.17 | +0.01 | 213 | −2.0 | 0.645 | 3.46 |
| 27 yr. | 168 | 0.112 | 0.094 | 2.04 | 1.93 | −0.30 | 193 | 1.0 | 0.355 | 2.58 |
| 138 yr. | 140 | 0.094 | 0.078 | 1.08 | 1.31 | +0.06 | 202 | 5.0 | 0.105 | 2.77 |
| | 114 | 0.093 | 0.101 | 1.56 | 2.39 | +0.69 | 184 | 8.3 | 0.557 | 3.11 |
| | 84 | 0.098 | 0.107 | 1.40 | 1.33 | −0.24 | 202 | 10.5 | 0.258 | 1.63 |
| | 49 | 0.094 | 0.101 | 0.58 | 1.48 | +0.75 | 218 | 13.0 | 0.461 | 2.67 |
| VI | 160 | 0.103 | 0.094 | 1.51 | 0.91 | −0.78 | 180 | −2.0 | 0.342 | 2.32 |
| 22 yr. | 132 | 0.107 | 0.106 | 1.30 | 1.76 | +0.27 | 188 | 1.3 | 0.489 | 3.20 |
| 110 lb. | 97 | 0.097 | 0.119 | 0.90 | 1.26 | +0.15 | 204 | 8.0 | 0.217 | 1.40 |
| | 76 | 0.090 | 0.094 | 1.06 | 1.59 | +0.38 | 213 | 13.3 | 0.560 | 3.60 |
| | 48 | 0.093 | 0.169 | 1.40 | 1.73 | +0.07 | 222 | 16.8 | 0.585 | 1.40 |
| II | 216 | 0.121 | 0.139 | 2.30 | 1.07 | −1.49 | 186 | 0 | 0.398 | ---- |
| 24 yr. | 185 | 0.104 | 0.125 | 2.15 | 1.06 | −1.38 | 179 | 3.0 | 0.624 | ---- |
| 101 lb. | 78 | 0.108 | 0.168 | 1.44 | 1.07 | −0.74 | 206 | 22.0 | 0.427 | 2.02 |
| VII | 46 | 0.086 | 0.336 | 0.91 | 1.86 | +0.71 | 242 | 27.0 | 1.226 | 8.40 |
| 23 yr. | 5 | 0.089 | 0.733 | 0.64 | 1.66 | +0.53 | 274 | 34.3 | 1.073 | 6.65 |
| 111 lb. | | | | | | | | | | |
| IV | 216 | 0.111 | 0.180 | 1.65 | 1.40 | −0.44 | 190 | −6.0 | 0.823 | 4.09 |
| 26 yr. | 156 | 0.113 | 0.147 | 1.32 | 1.27 | −0.27 | 184 | 0.8 | 0.627 | 2.69 |
| 138 lb. | 6 | 0.102 | 0.080 | 1.59 | 2.08 | −0.35 | 232 | 24.0 | 0.716 | ---- |
| X | 209 | 0.096 | 0.155 | 2.11 | 2.27 | −0.12 | 199 | 1.0 | 0.495 | 3.09 |
| 31 yr. | 41 | 0.100 | 0.275 | 1.60 | 1.27 | −0.58 | 242 | 28.0 | 0.784 | 3.45 |
| 144 lb. | | | | | | | | | | |
| XII | 44 | 0.101 | 0.122 | 1.01 | 2.16 | +0.89 | 231 | 25.0 | 0.552 | 3.46 |
| 21 yr. | 9 | 0.104 | 0.143 | 1.14 | 2.07 | +0.67 | 266 | 20.5 | 0.586 | 3.58 |
| 130 lb. | | | | | | | | | | |
| VIII | 84 | 0.112 | 0.237 | 1.40 | 2.08 | +0.31 | 212 | 16.0 | 0.550 | 3.02 |
| 33 yr. | 56 | 0.100 | 0.250 | 1.00 | 1.01 | −0.35 | 204 | 16.3 | 0.459 | 2.14 |
| 130 lb. | 27 | 0.081 | 0.177 | 0.83 | 1.68 | +0.57 | 219 | 19.5 | 0.228 | 2.28 |
| | 3 | 0.080 | 0.136 | 0.97 | 1.88 | +0.69 | 208 | 18.3 | 0.447 | 2.87 |

On the other hand it was apparent that serum calcium was somewhat dependent upon the net, and whatever the ultimate interpretation of the theory of calcium resorption into the bowel may be this relationship to net is confirmed because Fraction II is related to it in the same degree and way. The level of serum calcium therefore tended to decrease as retention increased in these subjects.

| | r | $P.E._r$ |
|---|---|---|
| Serum calcium and calcium balance | -0.44 | ± 0.09 |
| Serum calcium and Fraction II | -0.45 | ± 0.09 |

The correlation of +0.83 ± 0.04 between serum calcium and fecal calcium was of particular interest and showed that a fair degree of relationship existed between them. It will be recalled that the serum calcium was determined under fasting conditions during the time when the intestinal contents sampled as feces were being formed. Does this finding, then, support the theory of calcium resorption into the main channel of calcium excretion? In this connection it is of interest to refer again to the independence of serum calcium and calcium ingestion and the twenty-four-hour excretion of calcium into the maternal urine.

There was a very mild degree of correlation between the subjects' serum calcium and the stage in pregnancy which they had reached when these tests were made.

| | r | $P.E._r$ |
|---|---|---|
| Serum calcium and fecal calcium | +0.83 | ± 0.04 |
| Serum calcium and Fraction I | +0.32 | ± 0.11 |
| Serum calcium and stage in pregnancy | -0.33 | ± 0.11 |

*Urinary Calcium* (expressed in milligrams per c.c.).—In pregnancy, urinary calcium is of particular interest because of fetal-maternal relationships. No such correlation as was found between serum calcium and fecal calcium existed for urinary calcium and either fecal calcium or Fraction II. In each instance they were quite indifferently related. The urinary calcium was as independent of the ingestion as was the serum calcium. Likewise the chlorides and calcium were only remotely related.

The urinary calcium per cubic centimeter was somewhat dependent upon the oxygen consumption—a trend not seen in serum calcium. About the same degree of relationship existed between urinary calcium per cubic centimeter and phosphorus per cubic centimeter.

There was the same degree of correlation between urinary calcium per cubic centimeter and the stage in pregnancy as was seen for the latter and serum calcium per cubic centimeter, but they tend to be independent rather than dependent upon each other. This difference in relationship of course would be anticipated as a natural trend in fetal growth, although our subjects did not have a level of calcium ingestion theoretically yielding much surplus for maternal needs and fetal maintenance.

| | r | $P.E._r$ |
|---|---|---|
| Urinary calcium per c.c. and fecal calcium | -0.10 | ± 0.12 |
| Urinary calcium per c.c. and Fraction II | +0.17 | ± 0.11 |
| Urinary calcium per c.c. and calcium ingestion | -0.02 | ± 0.12 |
| Urinary calcium per c.c. and urinary chlorides | +0.23 | ± 0.11 |
| Urinary calcium per c.c. and stage in pregnancy | +0.30 | ± 0.11 |

*Fecal Calcium.*—In addition to the interesting manner in which the level of fecal calcium indicated the level of serum calcium, it was possible that a species of equilibrium existed between fecal calcium and oxygen consumption, for the level of fecal calcium tended to drop as the oxygen consumption rose. Fecal calcium had some degree of relationship to weight gain and increased as pregnancy progressed.

The fecal calcium had almost as clear a relation to weight gain during pregnancy as the balance (net) itself did, although it was independent of the absolute weight of the subject.

| | r | $P.E._r$ |
|---|---|---|
| Fecal calcium and oxygen consumption | −0.45 | ± 0.09 |
| Fecal calcium and weight gain | −0.44 | ± 0.09 |
| Fecal calcium and weight | −0.23 | ± 0.11 |
| Fecal calcium and stage in pregnancy | −0.61 | ± 0.07 |
| Calcium balance and stage in pregnancy | +0.60 | ± 0.07 |
| Calcium balance and weight gain | +0.50 | ± 0.09 |
| Calcium balance and weight | +0.54 | ± 0.09 |

*Fraction I and Fraction II Compared.*—Fraction I decreases as the oxygen consumption rises ($r = -0.60 \pm 0.07$), Fraction II and oxygen consumption tend to increase synchronously ($r = +0.61 \pm 0.07$). Fraction I decreases somewhat as the weight gain increases ($r = -0.41 \pm 0.09$), while Fraction II increases ($r = +0.55 \pm 0.09$. Fraction I is not closely related to stage in pregnancy ($r = +0.32 \pm 0.11$), Fraction II decreases in size as pregnancy progresses ($r = -0.67 \pm 0.07$) and predicts the net itself quite spectacularly ($r = +0.99 \pm 0.01$).

Apparently the urinary and gastrointestinal systems reacted differently in respect to calcium excretion. The serum calcium alone is somewhat affected by the level of Fraction II ($r = -0.45 \pm 0.09$), the urinary calcium is quite independent of it ($r = +0.17 \pm 0.11$). This finding confirms and is in accord with the relation demonstrated between fecal and serum calcium.

*Fraction III.*—Fraction III was designed to study ingestion and the calcium filtered by the kidney. It proved to have little relation to serum calcium, oxygen consumption, weight gain or stage in pregnancy. It correlated with the calcium balance well enough to be substituted very grossly for the net itself if fecal output were not known, but it is too easily affected by other elements to be of much value in studying any other phase of metabolism considered here.

| | r | $P.E._r$ |
|---|---|---|
| Fraction III and serum calcium | −0.15 | ± 0.11 |
| Fraction III and oxygen consumption | +0.35 | ± 0.11 |
| Fraction III and weight gain | +0.18 | ± 0.11 |
| Fraction III and stage in pregnancy | +0.15 | ± 0.11 |
| Fraction III and calcium balance | +0.70 | ± 0.06 |

*Weight Gain.*—It is evident from the preceding discussion that both serum calcium and urinary calcium were poor predictors of weight gain, nor did the levels of ingestion affect the gain very much. The fecal calcium, as was stated above too was somewhat lowered as weight increased, and it was about as good a predictor of gain as the entire balance or Fraction I which indicates the amount possibly available to the fetus.

The weight gain was more closely related to the oxygen consumption ($r = +0.88 \pm 0.03$) than to the absolute weight of the subjects ($r = +0.60 \pm 0.07$).

## GENERAL CONSIDERATIONS

In the preceding discussion paired relations were considered, some of which proved to be fairly significant. For several of the pairs, one would suspect that other factors might modify the degree of correlation

considerably. Therefore to get some insight into some points of doubt a partial correlation technique was used in order to see whether a third factor really influenced the result. The following relationships were studied.

*Serum Calcium and Balance, Weight Gain Held Constant.*—The correlation between the balance (net) and serum calcium was $-0.44 \pm 0.09$. This was raised to $-0.62 \pm 0.07$ when weight gain was taken into consideration. Apparently this relationship was affected by growth needs. This seems logical and could be said to indicate that the short-period sampling technique employed probably measured the intermittent trends in calcium utilization during pregnancy.

*Serum Calcium and Urinary Calcium, Oxygen Consumption Held Constant.*—The correlation between serum calcium and urinary calcium was $-0.24 \pm 0.11$. This was raised to a $-0.38 \pm 0.10$ when the oxygen consumption was held constant. Although neither relationship is close, the basal condition affected it.

*Serum Calcium and Fecal Calcium, Oxygen Consumption Held Constant.*—The correlation between serum calcium and fecal calcium was $+0.83$ and $\pm 0.04$. The figure changed only in the second decimal place when oxygen consumption was held constant, indicating that it had little effect upon the original correlation.

## INFERENCES

One can infer

1. That calcium may have been transferred from the blood stream into the bowel and that the levels in each were fairly closely related.

2. That the level of calcium in the food had little effect upon the amount of calcium carried in the serum. The net had some effect.

3. That the fraction of calcium possibly available to the fetus was affected by the oxygen consumption of the mother, bearing in mind that this fraction also contains calcium filtered from the maternal system by the kidney.

4. That measuring serum calcium level alone showed little regarding the ingestion level or the level of calcium in the urine during pregnancy.

5. That serum calcium determinations showed less about maternal weight gain during pregnancy than urinary, food or fecal calcium did.

6. That urinary calcium showed more about oxygen consumption than the level in serum, food and feces did.

7. That of the four calcium levels considered—serum, food, urinary, fecal—the fecal level was the most sensitive indicator of weight gain during pregnancy for these subjects, the urinary level being the most sensitive indicator of oxygen consumption.

8. That of the four types of "balance" considered—net, Fraction I, Fraction II, Fraction III—Fraction II predicts weight gain and oxygen consumption equally as well as net, and Fraction I predicts oxygen consumption just slightly better than either of them.

Since urinary calcium alone is better related to oxygen consumption than Fraction III and as well related as Fraction I, the level of fecal and urinary calcium alone is a fair indicator of the relation of the total calcium supply of the mother to some body needs and changes during pregnancy. The rate of change in each is of course not clarified enough by this study since it is based on pooled twenty-four-hour sampling.

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# A CASE OF FULL-TERM PREGNANCY WITH ACUTE SACCULATION OF THE UTERUS

ALFRED M. HELLMAN, M.D., AND HERBERT J. SIMON, M.D.,
NEW YORK, N. Y.

*(From the Service of the Sydenham Hospital)*

PATIENT, Mrs. C. F., twenty-three years of age, colored, was admitted to the Sydenham Hospital Aug. 22, 1936. Her last menstrual period was the first part of October, 1935. There was some spotting in November, 1935. The patient first became ill in the latter part of November, 1935, and was confined to bed with pain in her back and abdomen and continued spotting. In the last three months of her pregnancy she had some left lower quadrant pain and some vomiting. She had received no prenatal care but said that she felt fairly well throughout her pregnancy except as noted. She stated that she had not felt fetal movements for one week prior to admission. She had always been well and had never been operated upon, and considered herself a perfectly normal, healthy individual.

Physical examination revealed a rather poorly nourished, colored female, not acutely ill. Abdominal examination showed an enlargement the size of an eight months' pregnancy; the fetal parts were clearly felt. Her blood pressure was 100/75. The fetus was in breech presentation. No fetal heart could be heard, nor were fetal movements noted. The gravid womb had the typical "dead" sound of a dead fetus. X-ray confirmed the breech presentation and showed overlapping of the fetal skull bones. The Aschheim-Zondek test was negative. The blood Wassermann and Kahn tests were negative. The urine showed a faint trace of albumin but was otherwise negative. The blood count was normal with the exception of a secondary anemia. Vaginal examination revealed an elongated, tightly closed cervix; the presenting part was very high. Three separate attempts were made to induce labor with castor oil, quinine, and pituitrin, with no results. She was discharged from the hospital in fair condition on Sept. 7, 1936, and was told to report to the clinic regularly.

The patient was seen in the clinic on Sept. 10, 1936. The above findings were confirmed and a diagnosis of intraabdominal pregnancy was made. The important points that led to the making of this diagnosis were that the dead fetus seemed to be just under the abdominal wall, and that on bimanual vaginal examination a hard mass about the size of an eight weeks' pregnancy, seemingly an extension of the uterus, was felt to the right with the fetus above and to the left. It was de-

cided to inject lipiodol into the uterus to confirm the diagnosis. This was done and we were surprized to find that the lipiodol had easily ascended well into the abdominal cavity showing the fetal sac was connected with the uterine cavity. The patient was readmitted to the hospital Sept. 11, 1936, and after three days of rest and observation a laparotomy was performed. We realized that delivery from below would be impossible because of the long cervix and the large mass to the right blocking the pelvis.

On opening the abdomen a large, gray brown sac was seen, which obviously contained the fetus. The omentum was adherent to the sac over much of its anterior and superior surfaces. These adhesions were partially freed and the sac incised. There was little or no bleeding. The sac wall was friable and tore readily. The macerated nearly full-term fetus was extracted without difficulty. It was then seen that the fetus had been contained in a thin sac which arose from the fundus of the

Fig. 1.—View of entire gross specimen.

uterus. The sac was about 2 mm. in thickness and obviously fibrous in character. The placenta was attached to the mucosa of the uterus proper and the inner wall of the sac. Due to the poor condition of the patient a rapid supravaginal hysterectomy was done, the normal looking ovaries were left in situ, thus removing the uterus, sac and placenta in toto. The abdomen was closed in layers. During the operation an intravenous infusion of glucose and saline was given, and the patient left the table in fair condition. Shortly afterward she was transfused with 500 c.c. of whole blood. The patient's condition continued grave for twenty-four hours, and then she rapidly improved. She was discharged from the hospital on her sixteenth postoperative day.

A careful histologic study of the specimen was made. Figs. 1 to 5 illustrate our findings. A block of tissue was taken from the uterus proper, another from the junction of the uterus and the sac and a third block from the sac itself. These sections were studied with hematoxylin eosin and Van Gieson stains. We found an hypertrophied but otherwise normal musculature of the uterus in the first specimen. In the second specimen the transition from the normal musculature to fibrous tissue

could be seen, and in the third the predominant tissue was fibrous but there were still numerous uterine muscular fibers present.

The sacculation occurred on the fundus of the uterus to the left of the midline and in no way connected with either fallopian tube. The cavity of the sac was connected with the cavity of the uterus by an opening that admitted one finger easily, but no more. The placenta was attached almost entirely to the inner surface of the uterus, whereas the fetal membrane occupied the sacculated portion.

## DISCUSSION

It might be well to review in brief the facts of the history and the findings of the physical examination, which suggested to us that this was a case of abdominal pregnancy. We recalled the spotting after the first month of amenorrhea, the acute bed-confining illness in the second or third month of the pregnancy (the sac probably formed at this time); the vomiting and left lower quadrant pain during the last trimester of the pregnancy; the fetal death without even an attempt by the womb

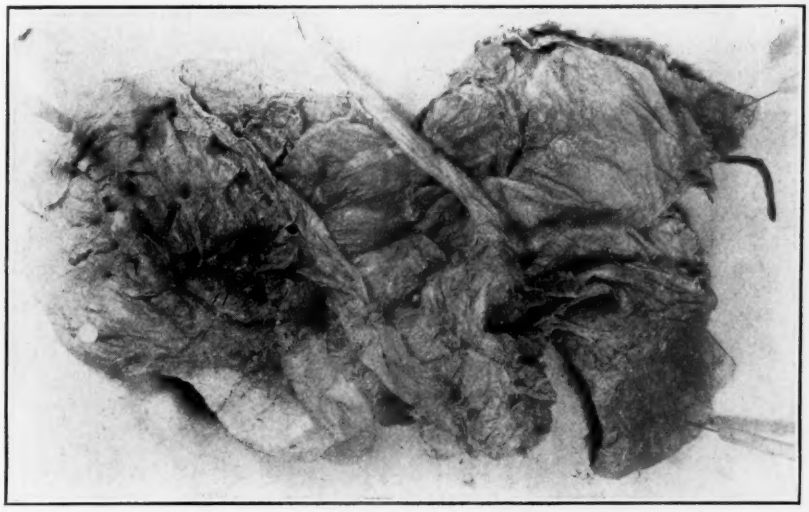

Fig. 2.—Another view of gross specimen.

to empty itself; the very high presenting part and the malposition; the ease with which we could palpate the fetal parts and the tightly closed and uneffaced cervix and the uterus to the right. Any three or four of these might strongly suggest an intraabdominal pregnancy; all of them together made us so sure that something was amiss, that in spite of the negative x-ray findings, it was decided to deliver this patient from above.

Shaw described a condition which he termed "acute sacculation of the uterus." In his case he found a sac coming off the fundus of the uterus, in which a four months' fetus lay. He refers to Döderlein's textbook on *Obstetrics,* in which it is stated that Freund, Schickele, and Hellendall have reported similar cases. All have definite explanations for the phenomenon. The most likely seems the explanation of Shaw himself, who suggests that as a result of failure of fusion of the müllerian ducts, there is some weakness in the uterine musculature.

In our previously reported case of extrauterine pregnancy, we thoroughly reviewed the literature on that subject. At that time no cases corresponding to this one were noted. We have, therefore, reason to believe that this case has its counterpart only in the cases reported by the authors listed above.

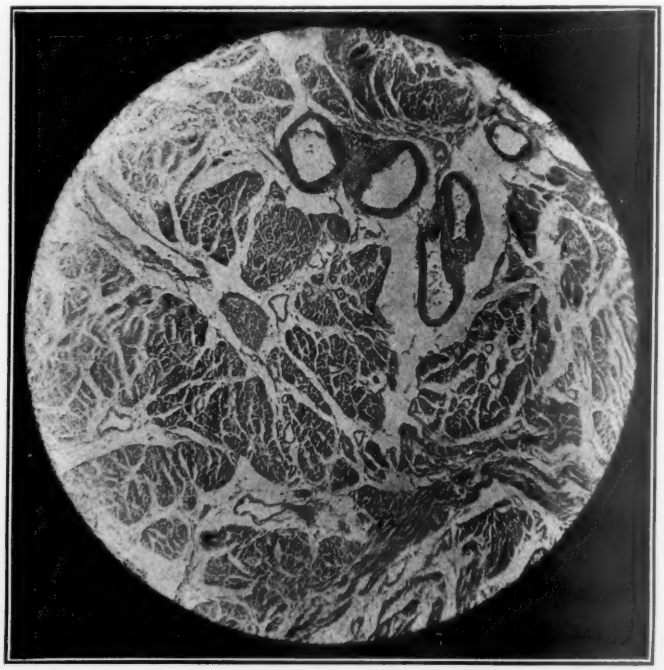

Fig. 3.—Section of uterine wall, showing much glandular tissue. (Van Gieson stain.)

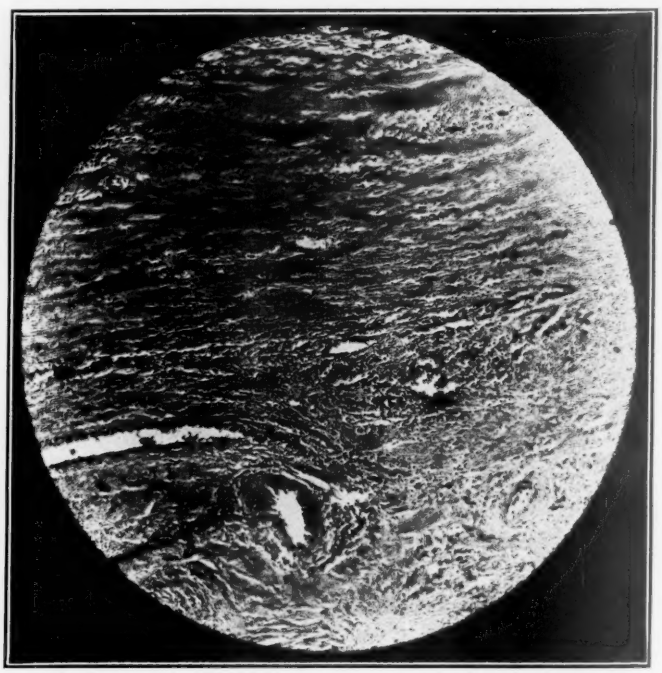

Fig. 4.—Section of the musculofibrous junction, Van Gieson stain, showing some muscle fibers and considerable fibrous tissue.

*Pathologic Report.*—(Dr. A. A. Eisenberg).—Specimen measured 23 by 19 cm., opened in operating room. External surface gray brown and had a rough appearance. Scattered throughout the external surface there were several flat elevations ranging in size from 2 to 3 cm. and presenting on section a white, coarse appearance. Over an area measuring 13 by 10 cm., the external surface was covered with omentum. The latter was adherent along the upper border of insertion. Otherwise it was free. The lower end of the specimen, apparently fundus, measured 6 by 3 by 5 cm. The remaining part of specimen was a thin-walled sac, measuring 16 by 16 cm. The width of the wall of the sac varied from 0.04 to 0.02 cm. On section through the wall, the blood vessels were wide open. The greatest part of the cavity was occupied by placental tissue. The amniotic membrane was gray brownish, semitranslucent and

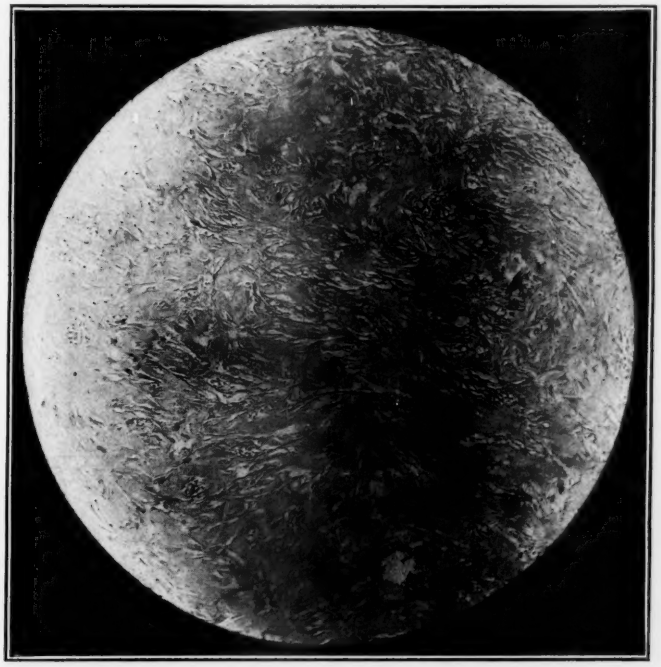

**Fig. 5.—Section of the wall of the sac, Van Gieson stain, showing large quantities of fibrous tissue and very few muscle fibers.**

measured in its widest diameter 22 cm. The placenta measured in its widest diameter 19 cm. and 14 cm. in its narrowest diameter. On section the placenta was flat and measured from ½ cm. to 1 cm. in thickness. The appearance of the placental tissue was pinkish. To either side of the placenta, the inner surface of the sac had a corrugated or flat nodular appearance and the color varied from gray to green and pink. On section the inner layer was gray brown, the outer layer was gray white. A piece of cord, measuring 24 cm. in length, was inserted eccentrically.

(A) Sections show homogeneous interlacing trabeculi of eosinophile tissue which enclose numerous capillary and sinusoidal vessels. Compressed and atrophic muscle fibers are intermingled with the eosinophile trabeculi; the atrophic muscle fibers usually border on the eosinophile tissue which predominates. (B) Sections show placental tissue resting upon a moderately wide layer of vacuolized muscle tissue. The placental tissue as well as the stroma of villi is here and there hyalinized.

Vascularity and cellularity of villi greatly decreased. (C) Sections show a wide layer of muscle tissue in the state of vacuolization and cloudy swelling. Inner surface is covered with necrotic placental tissue. (D) Sections show edematous bundles of smooth muscle fibers. Wall of blood vessels thin and surrounded by a collar of round cells. Here and there the muscle fibers show cloudy swelling and vacuolation. No endometrial lining found. (E) Sections show a wide layer of smooth muscle fibers with thin and wide fibrous septa. The muscle tissue fuses with an overlying layer of partly necrotic or hyaline placental tissue. (F) Sections present a picture identical with "A." (G) Lobules of fat tissue are loosely adherent to underlying structure which presents a picture identical with "F" and "A." The fat tissue is infiltrated with round cells. Above the trabecular layer there is edematous and disintegrating placental tissue. (H) Sections show fibromuscular tissue with muscle tissue predominating and with scattered areas of lymphocytic infiltration.

## SUMMARY

Thin part of uterus consists of trabeculae of hyalinized connective tissue interspersed with atrophic muscle fibers, thicker portion of wall consists of degenerated muscle.

## CONCLUSION

Because of the predominance of hyalinized connective tissue on one hand and the presence of degenerated muscle on the other, it is reasonable to assume that the uterine wall was structurally defective prior to pregnancy, that the myometrium was inadequately supplied with muscle fibers and that the pregnancy having occurred in a structurally weak uterus was instrumental in the dilatation thinning out and sac-like herniation of uterine wall.

*Pathologic Diagnosis:* Pregnancy in structurally defective uterus with herniation of uterine wall.

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44 East Seventy-Eighth Street
300 Central Park West

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**Cotte, G.: Remote Results in Autogenous Ovarian Grafts With Preservation of the Uterus,** Gynéc. et obst. **34:** 257, 1936.

In a series of ninety-two patients in whom adnexal or ovarian disease existed, the author preserved the uterus and performed autogenous ovarian grafts. Intraperitoneal sites, preferably the great omentum, were selected for transplants because subcutaneous locations proved less satisfactory and provoked cyst formation.

Activity of the graft most frequently becomes manifest about the third month postoperative. Reestablishment of menstrual function is the certain test of activity of the graft. Although the graft functions as the normal ovary, menopause occurs earlier. In more than half of the patients the periods were regular; in two cases excessive bleeding after a year of normal menstruation necessitated removal of the graft. The reappearance of periods in three patients operated upon after forty years of age is stressed as evidence that age is not an important factor.

Ovarian grafts performed in cases where acute adnexal disease existed were slower in functioning and had a briefer duration than those in which there was chronic adnexal disease.

Arnold Goldberger.

# THE CHEMICAL PREGNANCY TEST OF VISSCHER AND BOWMAN

WILLIAM J. MESSINGER, MAX H. PRESBERG, AND MARVEL-DARE FELLOWS,
ROCHESTER, N. Y.

*(From the Department of Obstetrics and Gynecology of The University of Rochester, School of Medicine and Dentistry)*

WITH the advent of the Aschheim-Zondek[1] test and its various modifications, the diagnosis of pregnancy has become more accurate. However, these tests are time consuming and expensive, thereby limiting their routine use.

In 1934, Visscher and Bowman[2] described a chemical test for the determination of pregnancy. This consisted of adding to 1 c.c. of urine 1 drop of 0.5 per cent hydrogen peroxide, 5 drops of 5 per cent phenylhydrazine hydrochloride, 5 drops of 5 per cent methyl cyanide and 5 drops of concentrated hydrochloric acid. This mixture was heated in a boiling water-bath for twenty-five minutes and the interpretation of the test was made on the color of the solution and the nature of the precipitate present. A russet color and a flocculent precipitate were interpreted as a positive test. A straw-colored solution and the absence or presence of a granular precipitate were considered negative. Visscher and Bowman made a correct diagnosis in 93 per cent of 317 urines from pregnant and nonpregnant women. They believe their findings comparable to results obtained with the rabbit ovulation test[3] which has an established accuracy of 95 per cent.[4] Their technic is simple and inexpensive, and it has the advantage of rendering a diagnosis within half an hour. Menken[5] in 1934, using the same technic, found, in a small series of cases, that the chemical test agreed for the most part with the clinical findings. Dolff[6] in 1935, in a series of fifty-four cases which were followed clinically, found that his results closely approximated those of Visscher and Bowman. With the exception of urines containing albumin and large amounts of reducing substances, these workers found the test to be quite reliable as a diagnostic procedure.

The purpose of this work is to attempt to confirm the findings of Visscher and Bowman[2] and to study the probable mechanism of their reaction. One hundred and eighty-seven specimens of urine from pregnant and nonpregnant patients were tested. Of this series, 118 were followed clinically for a sufficient length of time to establish a diagnosis; 69 of the 187 cases were checked with the rabbit ovulation test (Table I).

A correct diagnosis was made in 69.5 per cent of the total cases studied; 9.5 per cent gave false positive reactions; and 21 per cent were falsely negative in known cases of pregnancy. The chemical test agreed in 72.5 per cent of the 69 ovulation tests and gave 10.1 per cent false positive and 17.4 per cent false negative reactions.

TABLE I. ANALYSIS OF ALL DATA

| | NUMBER | PERCENTAGE |
|---|---|---|
| Total cases | 187 | 100.0 |
| Pregnant | 75 | 40.0 |
| Nonpregnant | 112 | 60.0 |
| False positives | 18 | 9.5 |
| False negatives | 39 | 21.0 |
| Correct diagnosis by chemical test | 130 | 69.5 |
| Total ovulation tests | 69 | 100.0 |
| Chemical tests agreeing with ovulation tests | 50 | 72.5 |
| False positive chemical tests | 7 | 10.1 |
| False negative chemical tests | 12 | 17.4 |

It is difficult to explain the discrepancy between our results and those of other investigators on the basis of old reagents, albumin, or reducing materials, all of which are known to decrease the accuracy of the reaction. In this study, reagents were prepared daily, and few of the false positives showed albumin or sugar (Table II). Why this reaction gave such a high number of incorrect results in clinically proved cases of pregnancy cannot be accounted for, at present.

TABLE II. ANALYSIS OF FALSE POSITIVE REACTIONS

| | |
|---|---|
| Without explanation | 13 |
| Albumin | 1 |
| Sugar | 4 |
| Total | 18 |

Dolff[6] reported that a positive chemical test could be obtained with prolan in concentrations varying from 50 rat units to as little as 0.8 mouse units. In this study, 4 c.c. of a standardized extract of the gonadotropic factor of the anterior pituitary gland containing 15 rat units per c.c. failed to give a positive test. Antuitrin-S (Parke Davis and Co.) in concentrations varying from 2.5 to 100 rat units likewise failed to give a positive chemical test. The potency of antuitrin-S was demonstrated by the fact that 0.5 c.c., equal to 50 rat units, readily produced ovulation in a rabbit.

The mechanism of the Visscher and Bowman test is believed by some workers[5, 6] to be in the nature of an oxidation-reduction reaction. Since diabetic urines were found to give false positive reactions, it was decided to determine the effect of various sugars on the chemical test. One to 10 per cent solutions of glucose gave a russet color and a granular precipitate. Considering the possibility that other urinary constituents enter into the reaction, known negative urines were made up to contain glucose in percentages ranging from one to ten. These still showed a negative chemical test, as did lactose and galactose solutions in concentrations of 0.05 to 4 per cent. The presence of a russet color with glucose solutions causes difficulty in interpreting results, but the absence of a

flocculent precipitate indicates that neither glucose nor the other sugars tested are responsible for the characteristic reaction obtained with pregnancy urines.

The question arose as to whether creatine (a known constituent in the urine of many pregnant women) was responsible for the positive chemical reactions obtained. Creatine was therefore added to known negative urines so that each cubic centimeter contained 1 to 2 mg., but no russet color or flocculent precipitate appeared. Histidine is another substance present in varying amounts in urines of pregnant women. Aqueous solutions of *d-l* histidine hydrochloride were employed in concentrations varying from 1 to 7 mg. per c.c. All of these tests gave a negative reaction as manifested by the presence of a straw-colored solution in which a finely granular precipitate was found.

Dilute solutions of albumin gave a dark red solution and a flocculent precipitate which definitely interfered with the interpretation of the reaction. Menken[5] reported that he had seen a flocculent precipitate in only a few cases and made his diagnosis mainly on the color of the reaction. Analysis of the data here indicates that urines considered positive on the basis of a russet color alone, without the presence of a flocculent precipitate, would be incorrectly reported in 75 per cent of such cases. In definitely positive reactions, a heavy flocculent precipitate was always obtained, and in weaker reactions a granular-flocculent precipitate. Therefore the presence of a flocculent precipitate is definitely necessary before a urine can be called positive by this test.

All attempts to confirm the titration method described by Visscher and Bowman[2] gave unsatisfactory results. Since it was practically impossible to read a sharp, definite end point, no correlation could be found between the titration values and the presence or absence of pregnancy.

## SUMMARY

1. Of 187 urines examined by the technic of Visscher and Bowman for the determination of pregnancy, 69.5 per cent agreed with the clinical diagnosis.

2. Approximately 9.5 per cent of the 30.5 per cent of incorrect chemical reactions were false positives and 21 per cent false negatives.

3. The chemical test agreed with the Friedman modification of the Aschheim-Zondek test in 72.5 per cent of the 69 cases.

4. The specificity of this test for anterior pituitary-like substance in the urine of pregnancy, capable of producing ovulation in rabbits, could not be established.

5. A russet color and flocculent precipitate could not be obtained with histidine, creatine, glucose, lactose, or galactose, which indicates that these substances are not responsible for the reaction.

6. A russet color and a flocculent precipitate should be present before a test be considered positive.

7. The titration method described by Visscher and Bowman in their original article could not be confirmed.

The authors express their gratitude to Dr. C. A. Elden for his cooperation and suggestions in this work and for his help in the preparation of the manuscript.

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## RESULTS WITH THE VISSCHER-BOWMAN PREGNANCY TEST

Robert D. Dunn, M.D., and Frederick J. Northway, A.B.,
San Francisco, Calif.

*(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine, and The Department of Public Health)*

INVESTIGATORS have again turned to the field of chemistry in their search for a dependable, simple, and quick procedure for the determination of pregnancy. Earlier efforts proved difficult as well as unreliable, and chemical methods were abandoned for the accurate but more expensive and time-consuming biologic tests originally introduced by Aschheim and Zondek and later modified by Friedman. Visscher and Bowman have recently described a chemical test which has considerable promise. Like the biologic methods, it is based upon the presence of the gonadotropic hormone in urine of pregnant women, and, according to Dolff, the chemical reaction taking place in this test depends on the oxidation of the anterior pituitary-like hormone. The procedure is inexpensive, rapid, and simple, and is carried out as follows: To 1 c.c. of urine are added 1 drop of 1 per cent hydrogen peroxide, 5 drops of 1 per cent aqueous solution of phenylhydrazine hydrochloride, 5 drops of 5 per cent aqueous solution of methyl cyanide, and 5 drops of concentrated hydrochloric acid. The mixture is then heated in a boiling water-bath for twenty-five minutes. The test is positive for pregnancy if a russet color develops and a flocculent precipitate appears. A straw color, with or without the presence of a powdery precipitate, indicates a negative reaction. Finer gradations of these reactions were described by Dolff, as follows: strongly positive, dark red brown with a heavy, flocculent precipitate; positive, red brown with a slight, flocculent precipitate; weak positive, or suspected, brown with a light, powdery precipitate; negative, clear yellow with no precipitate. We, also, have observed these graduated readings, and consider them important.

Visscher and Bowman tested 317 known pregnancies in this manner and obtained a correct reaction in 295, or 93 per cent. They also compared their test with the Aschheim-Zondek test in 40 clinically suspected pregnancies. The two methods corresponded in 33 instances and conflicted in 7. Of the latter, 3 gave positive chemical but negative Aschheim-Zondek tests; one nonpregnant patient known to have a uterine fibroid gave a negative chemical and a positive Aschheim-Zondek test; and 3 cases were not clinically controlled.

In Dolff's report on 83 patients, correct tests were recorded in 96 per cent of known pregnancies, 95 per cent of early pregnancies, and 82 per cent of ectopic pregnancies. In nonpregnant patients he obtained a negative reaction in urines of low specific gravity and a positive reaction in those of high concentration, but his figures for this group were not reported. He interpreted these false positive reactions as being due to an increase of catabolic products in the urine.

In a very small series of cases Menken reported a close correlation of clinical and chemical findings in both late and early pregnancy. In more recent observations, Dodds found the test correct in 90 of 100 pregnancies. Her report also included 80 nonpregnant gynecologic patients, 89 per cent of whom gave a negative test. The author recorded the diagnosis of the patients with false positive reactions but failed to cite their temperatures.

We have made Visscher-Bowman tests on 395 urines. Of 250 patients clinically proved pregnant, 212, or 84.8 per cent showed a positive reaction. We studied 65 patients in whom pregnancy was suspected by both Friedman and Visscher-Bowman tests. Of 41 patients giving positive Friedman tests, we obtained 36 positive and 5 negative Visscher-Bowman reactions; and in 24 patients giving negative Friedman tests we found 21 negative and 3 positive chemical reactions, a correlation of 87.6 per cent. A clinical follow-up of the latter group showed the Friedman tests to have been 100 per cent correct.

Since Dolff found that false positive reactions were likely to occur in urines high in catabolic products, we investigated the urines from 62 nonpregnant gynecologic patients. False positive reactions were obtained in 45.2 per cent of cases. Patients with fever, due either to in-

TABLE I

| | LATE PREGNANCIES (CLINICAL) | PER CENT CORRECT | EARLY PREGNANCIES (CLINICAL) | PER CENT CORRECT | SUSPECTED PREGNANCY, CHECKED WITH A-Z OR FRIEDMAN, AND CLINICAL FOLLOW-UP | PER CENT CORRECT | NONPREGNANCIES | PER CENT CORRECT |
|---|---|---|---|---|---|---|---|---|
| Visscher-Bowman | 317 | 93.0 | | | 37* | 92.0 | | |
| Dolff | 54 | 96.0 | 18 | 95 | | | | |
| Menken | 8 | 88.0 | 4 | 100 | | | 11 | 100.0 |
| Dodds | 100 | 90.0 | | | | | 80 | 89.0 |
| Dunn | 250 | 84.8 | | | 65 | 87.6 | 62 | 54.8 |

*Three of Visscher-Bowman's 40 cases were not clinically controlled, and therefore have not been included in this table.

fectious processes or postoperative reactions, made up the largest part of this group. The negative reactions (54.8 per cent) were found in afebrile patients. In the known pregnancies studied by us, correct findings were in urines with a specific gravity of 1.015 or higher, while approximately 90 per cent of the incorrect reactions occurred in more dilute urine. Essentially the same was true of urines from patients suspected of pregnancy. This observation we consider highly significant.

## CONCLUSIONS

Our results show a higher percentage of error than that recorded by other workers. Elimination of urines of low specific gravity and those containing undesirable catabolic products might better our results. In the suspected pregnancies, where these elements do not come into play, our findings were 87.6 per cent correct, the highest percentage of accuracy we found in any group. Contrasted with this, the fewest number of correct results (54.8 per cent) occurred in urines of nonpregnant *febrile* patients.

We must conclude from our results, as well as from the results of other investigators, that the Visscher-Bowman test for pregnancy is, as yet, not sufficiently reliable to supplant the biologic methods now in use. A modification of the technique, aiming at the elimination of the sources of error, may ultimately yield a very useful diagnostic method.

## SUMMARY

1. Three hundred ninety-five urines were tested by the Visscher-Bowman method for the determination of pregnancy. Correct reactions were obtained in 84.8 per cent of 250 known pregnancies, 87.6 per cent of 65 suspected pregnancies, and 54.8 per cent of 62 nonpregnancies.

2. Urines of low specific gravity or containing unusual amounts of catabolic reducing agents tend to give false reactions.

3. The test in its present form is subject to too high a percentage of error to replace the Friedman and Aschheim-Zondek tests.

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# ANTUITRIN-S CUTANEOUS TEST FOR THE DIAGNOSIS OF PREGNANCY

ISADORE GERSH, M.D., DENVER, COLO.

*(From the Department of Clinical Pathology, University of Colorado School of Medicine)*

NUMEROUS attempts have been made to develop procedures for the early diagnosis of pregnancy which are simpler and more rapid than the highly accurate Aschheim-Zondek and Friedman biologic tests. Recently the intradermal injection of anterior pituitary-like hormone has been revived by Gilfillen and Gregg[1] as a "new, rapid, economical test for pregnancy and certain gynecologic conditions."

Most of the previous reports in the literature concerning the value of the test have been unfavorable.[2] Since the recent encouraging report by Gilfillen and Gregg is so at variance with the previous literature, we have carried out a series of tests to determine the value of the procedure.

This study was carried out on 113 individuals. Fifty were normal men and nonpregnant women; 48 were known cases of pregnancy of two or more months' duration and fifteen were from one to nine days postpartum.

Each subject received three intradermal injections; two of which were different preparations of the hormone, namely (1) antuitrin-S which is an extract of pregnancy urine prepared by Parke, Davis & Co., and (2) an anterior pituitary-like hormone extracted from placental tissue.* These have apparently identical physiologic effects but are derived from different sources. The third injection was a control consisting of normal saline with 0.5 phenol. Each injection amounted to two minims. In order to check the possibility of differences in reaction to preparations of separate dates, antuitrin-S from three lots and placental anterior pituitary-like hormone from two lots of manufacture were used in this study.

The skin reactions were noted at intervals of one-half, one, and twenty-four hours following the injections. Results of the first two readings are shown in Table I. At the last reading, practically all subjects showed an area of erythema at the site of both the antuitrin-S and placental anterior pituitary-like hormone injections.

From the results it is evident that there exists a marked discrepancy between the skin reactions and the clinical diagnoses. The errors of the test consist in both false positive and false negative reactions. Using antuitrin-S, 20.8 per cent false negative results were obtained in our

*The author wishes to express his appreciation for this material to Dr. R. W. Whitehead, Department of Physiology and Pharmacology, University of Colorado School of Medicine.

pregnant patients and 6.6 per cent in the postpartum cases, while 81.6 per cent of the men and 66.6 per cent of the nonpregnant women showed false positive tests for pregnancy (based on skin reactions one hour after the injection). Furthermore, intradermal injections of phenolized normal saline gave definite erythematous reactions in 8.8 per cent of our subjects one-half hour after the injections and in 5.4 per cent at one hour.

TABLE I. RESULTS OF CUTANEOUS TESTS FOR PREGNANCY

| CLASSIFICATION | NUMBER EXAMINED* | POSITIVE CUTANEOUS REACTIONS | | | | PERCENTAGE OF ERROR | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ANTUITRIN-S (A.P.L.H., P.D. & CO.)‡ | | A. P. L. H.§ (PLACENTAL) | | ANTUITRIN-S (A.P.L.H., P.D. & CO.)‡ | | A. P. L. H.§ (PLACENTAL) | |
| | | ½ HOUR | 1 HOUR | ½ HOUR | 1 HOUR | ½ HOUR | 1 HOUR | ½ HOUR | 1 HOUR |
| Postpartum | 15 | 2 | 1 | 5 | 3 | 13.3† | 6.6† | 33.3† | 20.0† |
| Pregnant | 48 | 12 | 10 | 18 | 17 | 25.0 | 20.8 | 37.5 | 35.4 |
| Men | 38 | 15 | 7 | 24 | 17 | 60.5 | 81.6 | 36.8 | 55.3 |
| Nonpregnant Women | 12 | 7 | 8 | 10 | 10 | 58.3 | 66.6 | 83.3 | 83.3 |

*Saline controls yielding positive reactions at one-half hour, 10; at one hour, 6.
†Based on the assumption that these should yield negative cutaneous reactions.
‡A. P. L. H., P. D. & Co., Anterior pituitary-like hormone, Parke, Davis & Co.
§A. P. L. H., Anterior pituitary-like hormone extracted from placental tissue.

## CONCLUSIONS

In our hands the anterior pituitary-like hormone (antuitrin-S) cutaneous test for pregnancy was found to be entirely unreliable.

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**Rivoir, J.: Vaginal Secretion as a Cause of Primary and Recurring Cystitis,** Monatschr. f. Geburtsh. u. Gynäk. **105**: 344, 1937.

As emphasized by Rivoir, infection of the urethra plays an important rôle in inflammation of the bladder. The urethra is infected not only by the gonococcus but also by the staphylococcus, streptococcus, colon bacillus, etc. The author believes that about 70 per cent of women who have a chronic infection of the genitalia also suffer from a nonspecific infection of the urethra. Cystoscopic examination in these women demonstrates a trigonitis which, in the chronic cases, produces no noteworthy symptoms. Hence the author favors treatment of all vaginal discharges as a prophylactic measure against nonspecific infections of the urethra and trigonum.

J. P. GREENHILL.

# SKIN TESTS FOR PREGNANCY

CHARLES W. FRANK, M.D., AND PHILIP B. WAHRSINGER, M.D.,
NEW YORK, N. Y.

GILFILLEN and Gregg, in the September, 1936, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, presented a series of cases in which they found that "antuitrin-S, when injected intradermally, provides a reliable, simple, quick, economical, and accurate guide in the diagnosis of pregnancy." The theory propounded was that, since there is an anterior pituitary-like substance in the urine of pregnant women, pregnant women should not be sensitive to its intradermal application, and that nonpregnant women should show a dermal reaction to its injection. In other words, a positive skin reaction indicates the absence of pregnancy. The absence of a skin reaction indicates that pregnancy is present.

This pregnancy test was apparently first proposed by Porges and Pollatschek[1] of Vienna. It was subsequently investigated by Alfred Deutsch[2] in Europe and by Hyman Strauss[3] in this country. Both these workers found the test to be quite unreliable.

In order to verify the findings of Gilfillen and Gregg and to corroborate the above-mentioned theory, the following tests were done on a series of 198 cases on the Obstetric Service of Dr. Meyer Rosensohn, at The Bronx Hospital. Three different laboratory hormonal products were used. In all cases 0.2 c.c. was used intradermally on one arm while a like amount of sterile saline solution was used as a control on the other arm. In order to avoid pseudoreactions due to dermographia, infection, chemical irritation, such as alcohol, etc., only saline solution was used to cleanse the skin fifteen minutes before the test. Likewise, no product with an alcoholic base was used.

The first hormonal product used was antuitrin-S (Parke, Davis & Co.), an anterior pituitary-like substance derived from the urine of pregnant women. This was injected intradermally in 163 cases with the following results (Table I):

TABLE I

| TYPE OF CASE | TOTAL | SKIN REACTION | | |
|---|---|---|---|---|
| | | POSITIVE | NEGATIVE | DOUBTFUL |
| Prenatal (pregnant) | 112 | 28 | 76 | 8 |
| Medical (nonpregnant) | 22 | 21 | 1 | 0 |
| Postpartum (1 hour to 9 days) | 21 | 21 | 0 | 0 |
| Pediatrics (2 to 10 years) | 8 | 8 | 0 | 0 |
| Total number of cases tested | 163 | | | |

An analysis of this series shows that of 112 definitely pregnant women, 28 gave a positive skin reaction, falsely indicating that there was no

pregnancy present. Eight patients gave a doubtful reaction while 76 gave no reaction at all. In the pregnancy cases, therefore, the test was only 68 per cent accurate. Two of the postpartum patients were tested within one hour after delivery and both gave no skin reaction within the next hour; both, however, showed strongly positive reactions five to six hours later. A number of the positive skin tests lost their erythema within a few hours, but most of them remained red for one or two days. Almost all of the patients with positive skin tests complained of pain at the site of injection although there were no infections in the entire series. Of the nonpregnant patients, all showed definite skin reactions; some more positive (extensive) than others.

The second hormonal product studied was anterior pituitary luteum (Ayerst), an anterior pituitary-like hormone derived from the placenta. This substance was alcohol free. It was used in only six patients all of whom were definitely pregnant. The results are tabulated in Table II.

TABLE II

| TYPE OF CASE | SKIN REACTION | | | |
|---|---|---|---|---|
| | TOTAL | POSITIVE | NEGATIVE | DOUBTFUL |
| Prenatal (pregnant) | 6 | 2 | 3 | 1 |

In this small series, this product produced results only 50 per cent accurate, and its use was discontinued.

The third and final product studied was progestin (Upjohn) a corpus luteum extract from fresh glands containing corpus luteum hormone which plays such an important rôle in the physiology of pregnancy and menstruation. This was used in 29 cases with the following results, Table III.

TABLE III

| TYPE OF CASE | SKIN REACTION | | | |
|---|---|---|---|---|
| | TOTAL | POSITIVE | NEGATIVE | DOUBTFUL |
| Prenatal (pregnant) | 10 | 9 | 0 | 1 |
| Medical (nonpregnant) | 15 | 14 | 1 | 0 |
| Newborn (one to ten days) | 4 | 4 | 0 | 0 |
| Total number of cases tested | 29 | | | |

An analysis of this series shows that 98 per cent of all cases, including the pregnant women, produced a positive skin reaction rendering this test definitely inaccurate.

We must conclude, therefore, that the use of anterior pituitary-like hormone injected intradermally in the manner suggested by Gilfillen and Gregg, and scientifically controlled, in a series of 198 cases, did not provide an accurate or reliable skin test for pregnancy.

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# A STUDY OF THE "COLD TEST" IN NORMAL AND IN TOXEMIC PREGNANCY

DUNCAN E. REID, M.D., AND HAROLD M. TEEL, M.D., BOSTON, MASS.
*(From the Department of Obstetrics, Boston Lying-in Hospital)*

THERE is urgent need for some test or system of diagnostic procedures which would make possible the immediate and accurate classification of patients with hypertension, albuminuria and edema during pregnancy. Recognition of this need has led to the proposal of a number of tests, the purposes of which have been to distinguish between preeclampsia and eclampsia on the one hand, and vascular or renal disease independent of pregnancy, on the other. The common orthodox procedures are applications of tests used by internists to measure renal function. Among the more valuable of these are concentration and dilution of urine, phthalein excretion, blood chemistry, and urea clearance. If proper allowance is made for the peculiarities of the physiologic state of pregnancy (such as the tendency to retain water) these tests may be made to yield valuable information. However, they are of little or no positive value in the differentiation of essential hypertension, mild parenchymatous nephritis without significantly impaired renal function and preeclampsia. Further, they do not solve the problem of whether the increases which we so commonly see in the blood pressures (often accompanied by urine changes) of known hypertensives and nephritics during the last trimester of pregnancy are exacerbations of these diseases or the superimposition of preeclampsia.

Recently the "cold test" as described by Hines and Brown[1] has attracted considerable attention. These authors studied the response of the basal blood pressure to a standard cold stimulus from immersing the hand in ice water. They found that a characteristic exaggeration in the response to the test as measured by the rise in systolic and diastolic blood pressures was shown by 98 per cent of their patients with primary hypertension. Patients with hypertension due to nephritis failed to show this exaggerated response to the test.

Further, in a group of subjects with normal blood pressures, some 20 per cent showed an exaggerated response to the test. Of these individuals with normal blood pressures but with exaggerated response to the cold stimulus, the immediate family history was positive for hypertension or death from apoplexy in at least 75 per cent of the cases.

Thus, from the preliminary work of Hines and Brown, it appeared that their "cold test" might serve to differentiate hypertension due to parenchymatous nephritis from that due to vascular disease. Further, an exaggerated response in an individual with normal blood pressure seemed to suggest strongly a hypertensive diathesis (latent hypertension).

Dieckmann and Michel, and Randall and Murray were quick to see the possibilities of such a test as applied to the toxemias of pregnancy. In a preliminary paper, Randall and Murray[2] suggested that the test might reveal impending toxemia before the appearance of the classical signs. Dieckmann and Michel[3] also in a preliminary report, placed more emphasis upon the potential value of the test in prognosis and in differentiating between the acute toxemias and "chronic nephritis" by which they apparently mean both primary hypertension and chronic parenchymatous nephritis.

If there is practical value in the test, it would seem to us to lie in the aid it might give in prognosis and differential diagnosis as pointed out by Dieckmann and Michel. If it is true that the "cold test" will distinguish between primary and secondary hypertension, and will reveal latent hypertensive vascular disease; and if it is also true that responses to the test are not altered by normal pregnancy, obviously the "cold test" should be invaluable in the differential diagnosis of hypertension during pregnancy.

For two years we have used the "cold test" repeatedly upon a considerable number of both normal and toxemic patients during the course of pregnancy and in the puerperium. The technique which we have used in performing the test does not differ materially from that described by Hines and Brown. The patient assumes a comfortable reclining position, and the blood pressure is taken at intervals of a few minutes until a basal level is reached. This usually requires from ten to forty minutes. The opposite hand is then placed in an arm bath filled with ice water at 4° C. for two minutes. The blood pressure is recorded each thirty seconds during the period of the immersion and subsequently until it has returned approximately to the basal level. The maximum rise in systolic and diastolic pressure is taken as the response to the test.

The rise in blood pressure is apparently in response to the pain induced by the ice water. From experimenting upon ourselves and others, we have made several observations which have some bearing upon the interpretation of results. First, the subjective pain experienced varies to a considerable extent in the same individual when the test is repeated at different times although the conditions of the test remain constant. Second, the maximum pain occurs after some twenty-five to thirty seconds of immersion, and the hand subsequently becomes relatively numb. This observation is to be correlated with the fact that a maximum response in blood pressure is almost always

elicited by immersion of the hand for thirty seconds. The responses of the same individual to the test when it is repeated at intervals of several days are usually of the same general pattern although differences of 20 mm. Hg systolic in the maximum response are not infrequent. In our hands, the systolic response is more consistent than the diastolic when determined by the usual clinical sphygmomanometer and stethoscope.

In the original article of Hines and Brown, the average systolic and diastolic responses of the "normal" group of subjects were 8.62 and 8.14 mm. Hg. These authors regarded 15 mm. Hg as the maximum normal systolic response. Randall and Murray allowed 20 mm. Hg as a maximum normal systolic response. We have been able to confirm the observation that the response to the test is minimized or abolished by sedatives and anesthesia.

*Response to the "Cold Test" During the Course of Normal Pregnancy.*—The "cold test" was performed at intervals of from four to six weeks throughout pregnancy and puerperium upon 34 normal patients. In all, 159 observations were made upon this group of patients. None of them developed systolic blood pressures of 140 mm. Hg or more, or albuminuria or significant edema. The average rise of systolic and diastolic blood pressures in the different periods of pregnancy and puerperium in response to the "cold test" is shown in Table I. The individual variation in response to the cold fluctuated from three instances in which syncope developed with accompanying fall in blood pressure, to one instance in which the systolic rise was 62 mm. Hg. It will be seen from the table that although there is perhaps a slight tendency toward increase in response as pregnancy advances, such increase is probably not significant.

TABLE I. THE AVERAGE RISE IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN RESPONSE TO THE "COLD TEST" IN THE DIFFERENT PERIODS OF PREGNANCY AND IN THE PUERPERIUM. THE TABLE IS CONSTRUCTED FROM 159 OBSERVATIONS UPON 34 PATIENTS

| WEEKS DURATION | PREGNANCY | | | | PUERPERIUM | |
|---|---|---|---|---|---|---|
| | 8-16 | 17-24 | 25-32 | 33-40 | 1-2 | 6+ |
| Number of observations | 22 | 32 | 33 | 32 | 26 | 14 |
| Av. rise systolic blood pressure | 14.86 | 13.70 | 19.40 | 17.00 | 13.40 | 19.10 |
| Av. rise diastolic blood pressure | 10.63 | 11.06 | 9.20 | 10.90 | 12.90 | 18.00 |

Further examination of the results of the test in these 34 normal patients permits a number of interesting observations. (1) There were 4 subjects in whom the systolic response was always greater than 20 mm. Hg. Four or more tests at intervals of more than four weeks were done in each instance. The family histories in 3 of these patients were negative for hypertensive disease. We had the opportunity to personally check the blood pressures in the immediate families of two. (2) There were 16 patients or exactly half of the group in whom the

systolic response to the test on at least one occasion was greater than 20 mm. (3) The response exceeded 30 mm. systolic on one or more occasions in 8 patients. In only one of these latter cases was there a family history of hypertension.

*Response to the "Cold Test" During Toxemic Pregnancy.*—Five normal patients whose family histories were negative for hypertensive disease and whose past histories revealed no nephritis were followed from early pregnancy. Routine examinations included blood pressure, urinalysis, and weight, and in addition the "cold test" was performed at intervals of about six weeks on each patient throughout pregnancy. Each of these patients developed toxemia late in pregnancy. The "cold test" was performed eighteen times antepartum upon these 5 patients, and in only two instances were systolic responses greater than 20 mm. Hg obtained. One of these was obtained in a patient at the first test early in pregnancy when the blood pressure was normal. The responses of this same patient later in pregnancy were subsequently less than 20 mm. systolic even when the blood pressure was elevated due to toxemia.

Of 17 other patients who developed toxemia during pregnancy but whose blood pressures were normal both before the onset of toxemia and again postpartum, 11 showed systolic responses of 20 to 40 mm. Hg at the time of the toxemia. Thus, in 17 patients who may be fairly said to have had uncomplicated toxemias of pregnancy, there was no uniformity of response to the test.

*Response to the "Cold Test" During Pregnancy of Patients With Essential Hypertension.*—There were 14 patients upon whom "cold tests" were performed whose past histories, courses during pregnancy and follow-up examination for at least six months postpartum justified a diagnosis of essential hypertension. Only 6 of them showed systolic responses greater than 20 mm. Hg.

Pickering and Kissin[4] applied the "cold test" to a series of nonpregnant patients. Their results failed to confirm those of Hines and Brown that an exaggerated response to the test is characteristic of patients with latent or developed essential hypertension. Observations of our own upon a limited series of nonpregnant subjects are in accord with the findings of Pickering and Kissin.

## CONCLUSIONS

The results of our own study on normal and toxemic pregnant patients fail to support the suggestion that the test might reveal impending toxemia. Nor do we find the test of practical value in the differential diagnosis of pregnancy toxemias. Although the number of patients in our groups is too small to exclude a general relationship between the magnitude of the response to the test and essential hypertension or other forms of hypertension during pregnancy, the marked variations in response in

different patients of each clinical group, as well as considerable differences in the response of the same patient at different times, would exclude any value for the test in differential diagnosis for any individual case.

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# THE PRESENCE OF ESTROGENIC HORMONES IN MATERNAL AND FETAL CIRCULATION

S. D. Soule, M.D., St. Louis, Mo.

*(From the Department of Obstetrics and Gynecology, Washington University School of Medicine, the St. Louis Maternity Hospital and Barnes Hospital)*

THE problem of passage of substances through the placenta has been subjected to extensive investigation since the demonstration of the absence of anastomoses between maternal and fetal circulations.

Rupp[1] and Schlossmann[2] in authoritative monographs, discuss the permeability of the placenta to carbohydrates, proteins, lipoids, salts, hormones, vitamins, antibodies and antigens. Brandstrup[3] also notes that through the work of Slemons, Von Oettingen, Hellmuth, Runge and others, we now have quantitative data on various salts, glucose, urea, uric acid, creatine, creatinine, amino acids, proteins, lipoids and lactic acid.

The phase of this problem which has interested us most is the question concerning the presence of hormones in the fetal circulation. In a previous paper[4] the bibliography concerning the permeability of the placenta to various hormones was presented. Snyder, Snyder and Hoskins, Schlossmann and others have discussed the problem of transmission of adrenalin, insulin, posterior lobe of the pituitary and parathyroid extract. Soule[4] discussed the transmission of anterior pituitary or anterior pituitary-like hormones (Prolan B).

The literature concerning the presence of estrogenic hormone in the fetal circulation is meager. Schlossmann, quoting Courrier and von Loewe, concludes that female sex hormone (folliculin) is demonstrated in fetal blood. Skowron and Skarzynski,[5] working with rabbits, conclude that the placenta permits follicular hormone to pass through.

The most expedient method for the study of the interchange of substances between the mother and fetus is a comparative analysis of the maternal and fetal blood at the time of parturition. The approach to the problem in this laboratory is based on the simultaneous determinations of the presence of estrogenic hormone in human maternal and fetal blood.

Estrogenic hormone was determined by the Fluhmann method.[6] This test is based on the stimulation of the atrophied vaginal mucosa of the test animal (mouse). Whereas earlier tests utilized this principle by observing changes in the vaginal mucosa by smears, Fluhmann's procedure is dependent on "the histologic demonstration of certain changes in the vaginal mucosa of recently spayed mice which precede cornification, the most important of which is the formation of tall columnar cells secreting mucus (mucification)." Although this change was formerly thought to be a specific effect of a corpus luteum hormone, more recent investigation has demonstrated conclusively that mucification is an effect of estrin, and that the production of this change by corpus luteum extracts is due to the presence of small amounts of estrogenic hormone in these preparations. Thus mucification is recognized now as an estrogenic hormone response.

## METHOD

The animals used were young adult female mice, which had been spayed nine days prior to the onset of the test. For convenience to the operator the mice were spayed on Monday morning and were available for injection on the following Wednesday morning.

For this problem the test materials were blood samples taken from mother and child at the time of parturition. The mother's blood was obtained by venipuncture. The fetal blood was obtained by "milking" the cord before expression of the placenta. These blood samples were always obtained within the twenty-four hours immediately prior to the onset of the test. The samples were kept sterile; the clear serum separated by centrifugation and kept in the ice box. The time element is important in view of the possible variation of hormone content due to standing several days.

The previously prepared mice were injected three times daily; 0.5 c.c. at 9:00 A.M., 1:00 P.M., and 5:00 P.M., for three consecutive days. On the morning of the fourth day, the mice were killed and after abdominal incision and splitting the symphysis, the vagina was dissected free and fixed in formalin. The individual specimens were mounted in celloidin, sectioned at two or three levels and stained with hemotoxylin and eosin.

Because of the biologic variation in response to any one dosage, three or four mice were used for each determination. Thus this technique adhered closely to that originally published by Fluhmann.

The Fluhmann tests were performed using varying concentrations of maternal and fetal blood serums. In the earlier tests in the series, full strength serums were injected. The results revealed such a high concentration of estrogenic hormone, however, that subsequently both maternal and fetal serums were diluted with normal salt solution. Dilutions of 1:2, 1:4, 1:8, 1:16 and 1:20 were used. The maternal and fetal serums of any one set of injections were always of the same dilution.

## RESULT

As the concentration of estrogenic hormone in the tested serums became less, due to dilution, the degree of response became progressively lessened also. Thus, with the more dilute serums the type response was such as to allow for fairly delicate discrimination.

The degree of mucification as determined by the Fluhmann test was always the same in corresponding maternal and fetal serums in all dilutions.

The observation is most interesting when one recalls that most hormones are *not* found in similar concentrations on the two sides of the placental barrier.

### CONCLUSION

1. Estrogenic hormones are present in equal concentration in both maternal and fetal circulations.

2. The presence of estrogenic hormone in marked concentration in the fetal circulation is consistent with the clinical observance of enlarged breasts and bloody vaginal discharge in newborn infants.

3. Considering that there is no evidence that the fetus produces an excess of estrogenic hormone, we may assume that the placenta is permeable to estrogenic hormone.

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## THE VALUE OF CESAREAN SECTION WITH PORTES' TECHNIQUE IN THE PRESENCE OF INFECTION, WITH REPORT OF THREE CASES

Susanne R. Parsons, M.D., F.A.C.S., Santa Barbara, Calif.

*(From the Department of Obstetrics and Gynecology, Hunan-Yale Medical School, Changsha, China)*

THE treatment of frankly infected patients in whom delivery from below is either impossible or necessitates a destructive operation on a living child, has long been a matter of discussion. Classical section followed by supravaginal amputation of the uterus is usually considered the safest, but in a young woman, perhaps in her first pregnancy, it is far from ideal. Also the surgical risk to an exhausted patient is considerable. Transperitoneal or extraperitoneal section does not remove the source of infection, namely the uterus, and is not free from danger of subsequent peritonitis. Also almost the same surgical risk is encountered as with the amputation of the uterus.

In 1908 Sellheim suggested using a uterine-abdominal fistula in these cases. This allowed free drainage of the uterus and the abdominal cavity was protected by suturing the edges of the open uterus into the abdominal incision. A second laparotomy was necessary to return the uterus into the abdominal cavity. This operation seems to have been widely used in Germany. In 1924 L. Portes first suggested and used the "extériorisation" of the uterus in cases of infection. The technique consists briefly in delivering the entire uterus and adnexa intact through an ab-

dominal incision reaching from just below the xyphoid to just above the symphysis pubis. The abdomen is closed behind the uterus by through-and-through sutures. The uterus is then opened and the child delivered. The uterus and adnexa are allowed to remain on the abdominal wall for twenty to thirty days when they are replaced by a second laparotomy or the ''réintégration'' of Portes.

Döderlein[1] points out that this technique was suggested by Gottschalk in 1909 in the *Berliner Gesellschaft* and again in 1911 in Munich at the Gynaekologen-Kongress. It seems he did not use the operation, however. After Portes' original report in 1924 the operation was used widely in the Latin countries and later in Austria and Germany. In 1926 G. A. Wagner reported a small series of cases with good results, and in 1931 L. Kraul[2] reported one case with good result. His method differs in that he delivered the fundus of the uterus only so far as to allow the adnexa to remain within the peritoneal cavity. In this way he avoided closure of the tubes by granulation tissue incident to the weeks of extraperitonization and also the necessity of a second operation to replace the uterus. He sutured the unopened uterus laterally to the edges of the recti muscles. Here it remained and as involution took place, the uterus spontaneously sunk back into the peritoneal cavity. The result was a uterus fixed to the anterior abdominal wall after healing.

Kraul's method has the advantages mentioned of avoiding a second operation and closure of the tubes but it defeats the chief purpose of Portes' technique, namely removal of the uterus and adnexa from the peritoneal cavity until danger of spreading infection is past. Certain difficulties in Portes' technique should be pointed out, however. The acute anterior flexion of the uterus in lifting it through the abdominal wall and the necessary delay in delivering the child until the abdominal wall is closed may give rise to uterine apoplexy with resultant death of the child. The danger of peritonitis when the uterus is replaced is negligible if smears and cultures are taken before laparotomy. Poor union of the uterine wall is a more serious consideration in cases of union by second intention which is to be expected in such infected cases as demand this radical treatment.

It would seem to me that the bad points of Portes' technique are more than offset by the following advantages: A woman frankly infected who cannot be delivered from below may still be saved by cesarean section with very little danger of infection so long as the uterus and adnexa remain outside the peritoneal cavity during the first twenty to thirty days. The operation requires only a few minutes and may be used in patients who could not survive a longer more complicated operative procedure. Closure of the tubes may be largely overcome by the use of rubber tissue instead of moist gauze dressings. In this way the uterus and reproductive function may be preserved while minimizing the danger from infection while delivering through the abdomen.

These three case reports illustrate the use of Portes' technique where the patient was admitted late in labor, in extremis, frankly infected, and where delivery was impossible from below. Two are cases of deformity due to osteomalacia, one is a chondrodystrophic dwarf. In the first case wet gauze dressings were used. The tubes were completely closed by adhesions and granulation tissue. In the third case rubber protective was used and no gauze allowed to touch the uterus or tubes. Although the patient died after four days, there was no sign of granulation tissue formation, and it seems probable that this use of protective would decrease the incidence of closure of the fimbriated ends.

From the standpoint of puerperal infection the results in Cases 1 and 3 were satisfactory. In Case 1, there was an elevation of temperature from the fourth to the eleventh day, but the patient was feeling well, taking a general diet, the abdomen was soft and there were no signs of peritonitis, in spite of the fact that there was a drainage of huge quantities of pus from the uterus. After the eleventh day there

was no further elevation of temperature and the recovery was uneventful. In Case 3, the patient died on the fourth day, but up to this time showed no evidence of peritonitis or elevation in temperature.

All three patients were extremely bad surgical risks. In Case 1, which survived, the pulse was 120, blood pressure 104/60, temperature 37.2° C. In Case 2 the pulse was 140, blood pressure could not be obtained, temperature 35.5° C., and in Case 3 the pulse was 120, blood pressure 68/42, temperature 37.2° C. It was felt in each case that amputation of the uterus would not have been survived, while Portes offered a rapid delivery with little additional shock. In each case the condition after operation was no worse than when the patient went onto the table. In addition, as Cases 1 and 3 illustrate, infection was adequately cared for.

CASE 1.—(13406) Mrs. T. P. S., admitted to the Hunan-Yale Hospital Jan. 12, 1934, after being in labor eighteen hours. She was delivered of a living child in this hospital four years ago by cesarean section and warned that spontaneous delivery would be impossible. In spite of this she remained at home attended by a Chinese midwife until after the rupture of the membranes.

Past history was unimportant but for the fact that she did not walk until two years of age. There were no serious illnesses or accidents. Menstrual history was regular, onset at seventeen years, last period in April, 1933.

Physical examination showed a woman pale, sweating, cold, exhausted. Height was 132 cm., weight 97 pounds, temperature 37.2° C., pulse 120, blood pressure 104/60. Head and chest were normal. Abdomen was enlarged to the size of a term pregnancy. The fetus presented by vertex, no fetal heart heard. The head was not engaged and definite over-riding at the symphysis was evident. The pelvis measured: spines 20.5, crests 21, trochanters 24.5, Baudeloque's 16, tuber ischii 5 cm. The urine showed 2-plus albumin, red blood cells, and white blood cells. The red blood count was 4,100,000, white blood was 43,300, Hb 91 per cent.

X-ray of the pelvis showed diagonal twisting of the bones with extreme scoliosis of the lumbar spine. The sacrum was displaced to the right, the superior strait was triangular and irregular in shape, with the sacral promontory at the level of the symphysis but to the right of the midline. The diagonal conjugate measured 7 cm. The pubic arch was very narrow which further decreased the available space for delivery from below. Engagement in the superior strait was prevented both by the size and shape of the inlet.

The uterine contractions were every three to five minutes and forceful. Immediate delivery was necessary to prevent rupture of the uterus through the old scar. The outlet contraction was too great to permit of any destructive operation from below and the patient's condition forbade any prolonged surgery, as supravaginal amputation of the uterus after section.

Portes' section was done under ether anesthesia. The abdomen was opened by a long incision from just below the xyphoid to just above the symphysis. The skin was protected with towels and the uterus delivered intact. The abdomen was rapidly closed by through-and-through silkworm-gut sutures above and below the uterus, and protected with more thick gauze pads and towels to prevent contamination from the uterine contents. The fundus was incised and a dead macerated full-term fetus delivered. The placenta was expressed and the uterine incision closed in two layers, first interrupted, the second continuous catgut. The uterus was dressed with moist gauze, dry towels, and a tight abdominal binder applied.

The pulse remained between 120 and 130 during the operation and the patient was sent to her room in good condition. Voiding was spontaneous. Daily dressings with moist saline gauze were applied to the uterus. On the second day the temperature rose to 37° C., pulse 80. There was a further elevation of temperature on the fourth day to 37.8° C. and it continued between 37° and 38.6° C. until the eleventh day when it fell to normal and showed no further elevation during the stay

in the hospital. On the fifth day the uterus began to discharge foul pus which was very profuse, saturating the entire bed. The white blood count was 28,000, with 94 per cent polymorphonuclears. The uterine sutures sloughed out, leaving a gaping incision which, however, provided wide and safe drainage outside the abdomen, which remained soft and undistended. Dakin's solution was used to irrigate and dress the uterus. A general diet was taken and the condition of the woman was excellent.

Involution took place normally and by the nineteenth day culture showed only a few staphylococci present. Five days later, under local anesthesia the uterus was sutured and replaced into the abdomen. A mercurochrome cigaret drain was left in the uterus which was later removed through the vagina. The abdominal wall was closed in layers and the rest of the stay in the hospital was uneventful. Both tubes were closed by adhesions at the fimbriated ends and further pregnancy was not probable. Sterilization, however, was not done on account of the refusal of the husband and woman herself. The patient was discharged from the hospital Feb. 27, 1934, and seen May 7 in the dispensary when she was in excellent condition.

CASE 2.—(13537) Mrs. C. Y. S., admitted to the Hunan-Yale Hospital Feb. 5, 1934. The woman had been in labor for four days, 3 of which she had spent at home under the care of a native midwife. Twenty-four hours before admission she had been taken to a Chinese hospital where large doses of pituitrin had been injected.

The patient was a twenty-year-old primigravida. Past history could not be obtained other than that she had been blind for some years.

Physical examination showed a woman acutely ill, pale, sweating, pulse weak, 140 per minute, temperature 35.5° C., blood pressure not obtainable. Both eyes were blind and scars of old tracoma evident. The lungs were clear, heart sounds faint but no murmurs heard. The abdomen was enlarged to the size of a term pregnancy but the uterus was tetanically contracted over the fetus, making it difficult to palpate the fetal parts. The child presented by vertex, which markedly overrode the symphysis. No fetal heart tones were heard. No presenting part could be reached by the examining finger in the rectum and a foul meconium-stained fluid was being passed from the vagina.

The most striking point in the physical examination was the small stature of the woman whose height measured approximately 40 inches. The spine was twisted with a marked lumbar lordosis which had caused the promontory of the sacrum to descend downward and forward to the level of the symphysis, thus doubling the sacrum on itself. This gave a greatly decreased anteroposterior diameter to the sacrum with a diagonal conjugate also decreased to 6 cm. The sacral promontory lay directly behind the symphysis. The external pelvic measurements were, spines 23, crests 25, trochanters 25, Baudeloque's 16, and tuber ischii 7.5 cm.

The blood count was R.B.C., 4,780,000; W.B.C., 13,450; Hb 106 per cent; polymorphonuclears, 81 per cent. No urine was obtained on catheterization.

Although there was no history obtainable of a decrease in stature, the bony deformity was characteristic of osteomalacia.

The woman was at once given supportive treatment, heat, intravenous glucose, and saline hypodermoclysis. Using ether anesthesia she was prepared for laparotomy. A midline incision was made from the xyphoid to 15 cm. above the symphysis. The bladder was dark, hemorrhagic, and the lower uterine segment was of paper thickness, in places gangrenous. Extreme care was necessary in delivering the unopened uterus in order not to rupture the lower segment during the flexion. On this account the upper end of the abdominal incision was not sutured until after delivery of the child. Large gauze packs and towels were used to protect the upper abdomen from contamination by the uterine contents as well as the routine packing off of the lower incision. The tightly contracted uterus which outlined the body of the fetus like a

glove, was opened at the fundus in order to avoid the gangrenous lower segment. The child was grasped by the feet and peeled out of the uterus. It was full term, stillborn, and macerated. The placenta was removed and the uterus wiped clean of membranes. The uterus was rapidly sutured in two layers and all dressings removed and the gloves changed. With fresh instruments the abdominal wall was now closed by through-and-through silkworm-gut sutures, both above and below the uterus which was allowed to remain on the surface. The uterus and adnexa were covered by rubber tissue and wet gauze dressings.

The operation lasted twenty minutes and the pulse remained 140 throughout, was small but regular. Fluids were continued with small amounts of ephedrine and digitalis given during the next ten hours. Transfusion was not possible on account of lack of donors, and the patient died ten hours after operation of cardiac failure.

The child weighed 5 pounds. The head measured S.O.B. 9 cm., Bip. 9.5 cm., O.F. 11 cm., O.M. 10.5 cm.

CASE 3.—(13756) Mrs. H. L. S., a primigravida, was admitted to the Hunan-Yale Hospital March 13, 1934, after being in labor for four days. She had been attended by several midwives and the membranes had been ruptured for two days. She could give little past history other than that she had always been small. She was employed as a monkey trainer in a Chinese circus. Her husband was of normal height and physical development. No other members of her family were said to be unusual in any way.

Physical examination showed a woman 132 cm. in height, heavy muscular development, but the bony conformation of a typical chondrodystrophic dwarf. The head was markedly brachycephalic with prominent forehead and saddle nose, the arms and legs were short with great bowing of the tibia.

The patient was exhausted. Labor pains were almost continuous. The temperature was 37.2° C., pulse weak, small, 120 per minute, blood pressure 68/42. Head, heart, and lungs were essentially negative. The abdomen was tense, the uterus tetanically contracted with the fundus lying under the diaphragm on account of the short torso. The child presented by vertex and was estimated at 7 pounds. No fetal heart was heard. The pelvis measured: spines 21, crests 23, trochanters 29, Baudeloque's 14.5, and tuber ischii 6.5 cm. Rectal examination showed the membranes ruptured but only the finger tip could be inserted between the symphysis and the sacral promontory, which lay directly behind the symphysis. The R.B.C. was 3,540,000; Hb, 75 per cent; W.B.C., 24,700; polymorphonuclears, 94 per cent. Urine showed a one-plus albumin with granular casts.

Delivery from below was, of course, impossible with the diagonal conjugate of less than 2 cm. The patient was frankly infected and so poor an operative risk that amputation of the uterus after section was not to be considered. Therefore Portes' technique was decided upon as offering the least surgical shock and at the same time taking care of the infection. Under ether anesthesia the abdomen was opened from 6 cm. below the xyphoid to just above the symphysis. The uterus was found tightly contracted over the fetus and was delivered intact. A contraction ring was found about the neck of the child with the head fixed below the ring. The abdomen was rapidly closed above and below the uterus by through-and-through silkworm-gut sutures and protected by towels and gauze from contamination. The uterus was incised in the midline and it was necessary to carry the incision downward through the contraction ring before it was possible to free the head. The child was full term, macerated, stillborn, but showed no evidence of chondrodystrophy. The placenta was removed and the uterus closed in two layers. The tubes were excised by wedge-shaped incisions and the distal ends buried in the folds of the broad ligament. The uterus was then protected by rubber tissue and dressed with warm moist gauze. The operation required thirty-five minutes in all, and the pulse was

136 as the patient was returned to her room. Digitalis and ephedrine were given and fluids by vein and subcutaneously, as well as by rectum.

A few hours after operation the temperature rose to 38.8° C. and the pulse to 150, but the next day the temperature was 37.2° C., pulse 120. Fluids were taken well and there was no distention. The second day the dressings were changed. The uterus was clean and no bleeding. On the fourth day the general condition was worse, the temperature was 37° C., respiration was shallow, and the pulse weak, 130 per minute. Involution had begiun and the abdomen showed no evidence of peritonitis. In spite of intravenous glucose, digitalis, and general supportive treatment, the patient died four days after delivery of cardiac failure. The hemoglobin at this time was 82 per cent. X-ray of the pelvis showed an anteroposterior contraction with the sacral promontory almost touching the symphysis. X-ray of the child showed normal bony development.

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## TISSUE LOSS FROM THE ENDOMETRIUM DURING MENSTRUATION

MELVILLE C. WATSON, M.D., AND EARL W. MCHENRY, M.D., PH.D.,
TORONTO, ONT.

HERETOFORE, the description of the changes in the endometrium which characterize the normal menstrual cycle in the human female has been inadequate, in as much as the reason for the death and the dissolution of the cells in the endometrium which results in macroscopic tissue loss, has not been explained.

The observations reported here are based on the first experiment in an investigation which is intended to justify the following conclusion, namely: during the functional stage, the internal economy of the epithelial cells in the endometrium is so altered by the accumulation, within the cell, of the elements of the secretion to be elaborated, that a return to their former state after the stimulus to the formation of secretion has been withdrawn is impossible. Therefore when the stimulus from progestin disappears with the normal degeneration of the corpus luteum at the end of the cycle, these functioning cells die, and dissolution of the cells with tissue loss results.

The development of the endometrium in two monkeys was artificially augmented by the administration of estrone and progestin. Each animal received simultaneously a hypodermic dose of 1 mg. of estrone in oil daily for seven days followed by a hypodermic dose of four rabbit units of progestin daily for five days. A hysterectomy was performed on animal "A" on the day following the last dose, and on animal "B," on the fifth day following the last dose of progestin. The uterus in each

case was manipulated during the operation by grasping the uterine ligaments and the organ was immediately transferred to the fixing fluid.

The photographs shown in Figs. 1, 2, and 3, are of sections from the uterus of animal "A." Fig. 1 represents a cross-section of the uterus from a position close

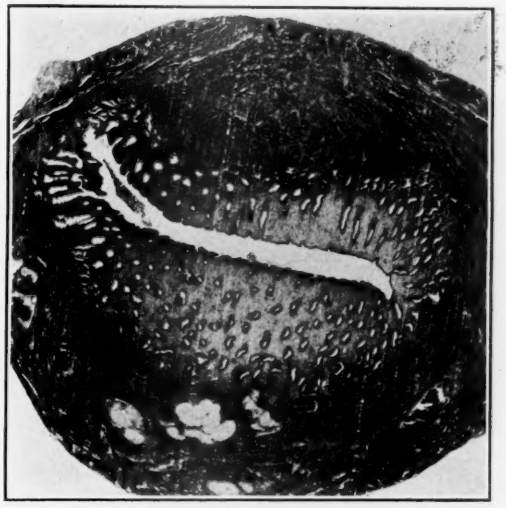

Fig. 1.

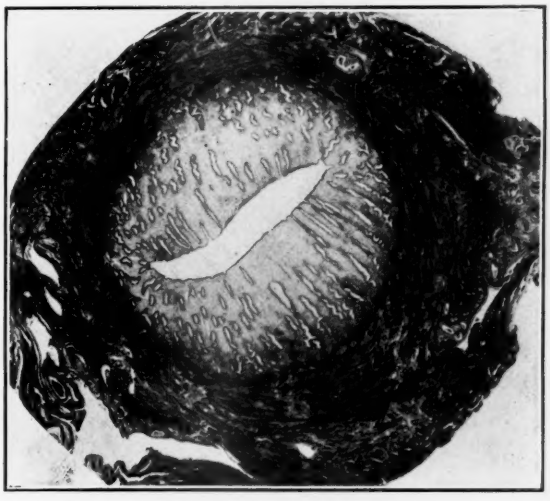

Fig. 2.

to the fundus, and accordingly most of the glands in this photograph are shown in cross-section. Fig. 2 is a photograph of a section taken 4.5 mm. lower in the uterus than Fig. 1, and Fig. 3 is from a section 4.5 mm. lower than Fig. 2. These photographs show clearly that the endometrium in this uterus was in a well-developed functional stage and that it had remained intact because the epithelial lining of the lumen of the uterus was uninterrupted throughout.

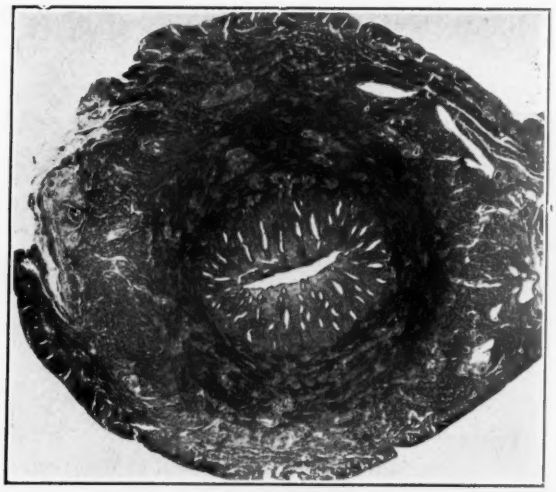

Fig. 3.

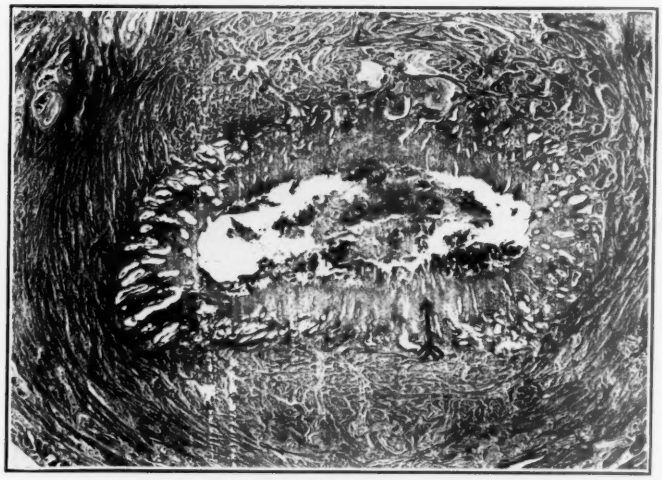

Fig. 4.—The arrow marks the position of the section shown in Fig. 9.

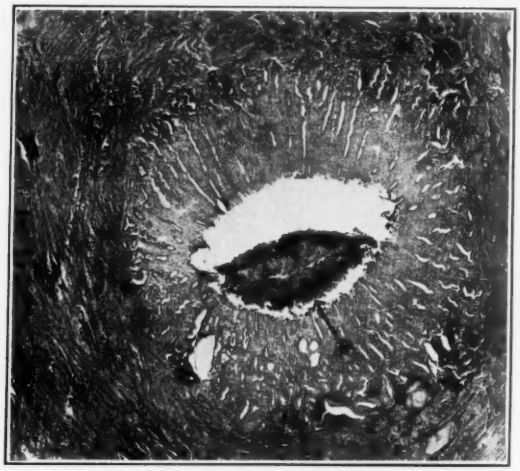

Fig. 5.—The arrow marks the position of the section shown in Fig. 8.

The photographs shown in Figs. 4, 5, and 6 were taken from sections of the uterus of animal "B." These photographs show the endometrium as it appears during the process of cellular dissolution and tissue loss after progestin therapy had been discontinued for a period of five days. In Fig. 4 the major portion of the outline of the original lumen of the uterus can be seen in the center of the mass of de-

Fig. 6.—The arrow marks the position of the section shown in Fig. 7.

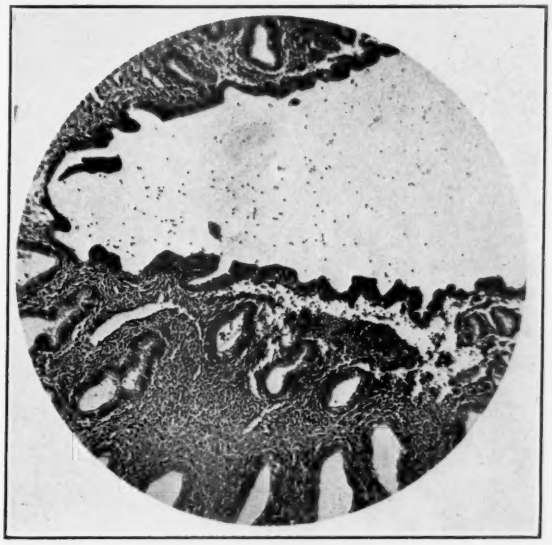

Fig. 7.—Tissues beginning to lose definite outlines in area with extravasation of blood. (×250.)

generating tissue occupying the newly formed cavity. Dissolution of the epithelial and the stroma cells in this central mass is very complete. In some areas in this degenerating mass the outline of a gland can be recognized but individual cells in the epithelium of these glands cannot be made out. The epithelium of the glands in the superficial area surrounding the new cavity also shows evidence of fairly com-

plete dissolution, although hemorrhage into the stroma surrounding these glands is not a marked feature. Fig. 9 is a photomicrograph showing marked degeneration in the epithelium of the glands at the position marked in Fig. 4.

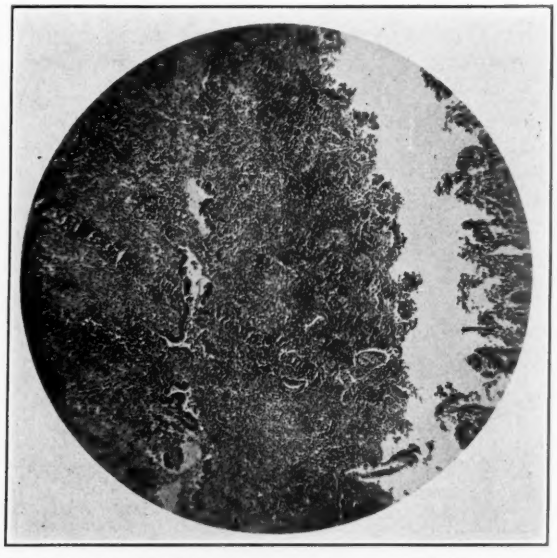

Fig. 8.—Epithelial and stromal cells in the area have completely disappeared. (×250.)

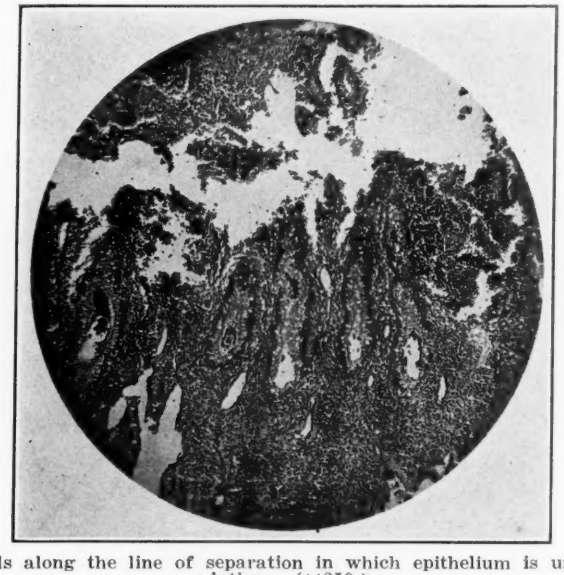

Fig. 9.—Glands along the line of separation in which epithelium is undergoing dissolution. (×250.)

The central degenerating mass in Fig. 5 is again a complete cast of the original lumen of the uterus. The epithelium which originally surrounded the lumen of the uterus is still recognizable in certain areas as is shown by higher magnification in the center of Fig. 8. While free red blood cells are very numerous in the degenerating mass shown in the center of Fig. 5 there is very little hemorrhage into

the stroma where the endometrium is still intact. This observation lends support to a speculation that the hemorrhage which occurs during menstruation may be secondary to the death and dissolution of the tissues.

Fig. 6 is a photograph of a section close to the internal os from the same uterus showing very superficial dissolution in the endometrium. The epithelial lining of the lumen in this section is still intact, the epithelial cells of the glands in the degenerating area are quite indistinct and there is a very limited amount of free blood in the area.

## CONCLUSIONS

The dissolution of the epithelial cells in the superficial glands of the endometrium in animal "B" is similar to the dissolution of the functioning epithelial cells which we have observed in the glands of the endometrium in the human female following a similar course of treatment with estrone and progestin. Dissolution of epithelial cells in the normal endometrial cycle, only occurs in the epithelium of the glands which have been stimulated to a full functional stage, and then only when the stimulus to function has been withdrawn. Tissue loss from the endometrium during normal menstruation is limited to the epithelium of the glands which have been fully activated by progestin and to the stroma which supports those glands.

The authors are indebted to the Connaught Laboratories for permission to carry out this work and also for gratuitously supplying the estrone which was used. Grateful appreciation is also extended to Professor W. A. Scott for his helpful interest.

We are indebted to the Banting Research Foundation for a grant to one of us (M. W.).

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**Golub, L. J., and Shelanski, H. A.: Silver Picrate Treatment of Vaginal Trichomoniasis,** J. Lab. & Clin. Med. 22: 1155, 1937.

These authors have treated 25 patients having *T. vaginalis* with a 1 per cent dispersion of silver picrate in kaolin applied to the vagina with an occluding insufflator; this treatment was followed by a course of six suppositories each containing 2 gr. of silver picrate—one inserted every night starting one day after the insufflation. The patient then returned in one week for another course of insufflation followed by the above suppository treatments. Two such courses of treatment were the usual routine, but in some cases more treatments were required. After each menstrual period, patients were reexamined and the treatment repeated if necessary. The cervical mucous plug must be removed to prevent reinfection. For this purpose a colloidal aluminum hydroxide gel plus kaolin was used; this was followed by cleansing the cervix and vagina with sterile water, the latter being less irritating than green soap. Intercourse, douches and tub baths are to be avoided; hygienic measures are also important.

Methods of transmission are discussed, including the presence of *T. vaginalis* in prostatic fluid, which was responsible for recurrence of symptoms in three cases.

W. B. SERBIN.

# PREGNANCY IN LYMPHOPATHIA VENEREA, COMPLICATED BY ESTHIOMENE AND RECTAL STRICTURE

I. D. Michelson, M.D., Joseph G. Crotty, M.D., and
Lyman A. Kasselberg, M.D., Memphis, Tenn.

*(From the Departments of Gynecology and Bacteriology, University of Tennessee, and the John Gaston Hospital)*

THE Frei reaction is generally accepted as the definite criterion of existing or past infection with the filtrable virus of lymphopathia venerea. A positive reaction depends upon sensitization of tissues to the virus or its by-products. While generally regarded as a localized disease, there are investigators[1, 2] who, on the basis of experimental and clinical findings, view this entity as a generalized infection with local manifestations at the portal of entry. The results of numerous Frei tests show that in the female, stricture of the rectum and esthiomene or elephantiasis of the vulva usually result from invasion of this virus. Stricture of the rectum is the common manifestation of the disease, Lichtenstein finding esthiomene in only six of 58 cases.[3]

In the rather voluminous literature dealing with various aspects of this condition the effect of the disease on fecundity and pregnancy has been almost entirely neglected. Wilson[4] in 1930 reported a number of cases of granuloma inguinale associated with pregnancy. One of the patients also had an elephantiasis of the vulva, but no Frei test, which might have established a diagnosis of lymphopathia venerea, was performed. The same objection must be raised in the case report of Das[5] describing elephantiasis of the vulva associated with pregnancy, because again no Frei test was done. Recently Gaines and McDowell[6] described a case of rectal stricture and pregnancy, but again no mention of a Frei test is made. We wish to report a case of lymphopathia venerea with the clinical manifestations of elephantiasis of the vulva and stricture of the rectum with a positive Frei reaction, and to emphasize certain interesting laboratory findings, which may have differential value, if found to exist in all patients suffering from this condition.

## CASE REPORT

M. J., thirty-four-year-old negro female, was first seen in the Out-Patient Department of the John Gaston Hospital on April 6, 1926. A diagnosis of chronic salpingitis was made at this time. Due to hemolysis the blood Wassermann was not determined. She next visited the clinic in October, 1927, with the same complaints. The blood Wassermann on this occasion was four-plus. A course of antisyphilitic therapy was instituted, but in May, 1928, the Wassermann was still positive. When seen again in November, 1929, she complained of arthritis in the left knee, but a cervical smear was negative for gonococci. She was now placed on a course of mercury, which was followed rather irregularly until August, 1930. She reappeared in the clinic in February, 1936, and the blood Kahn was now negative. An hypertrophy on the vulva was noted for the first time. On Aug. 28, 1936, she was admitted to the Gynecology Service of the John Gaston Hospital for study of the genital lesion.

The growth on the genitals was first noted three years ago. Redness, tenderness, or acute pain was never present. The swelling has progressively increased in size with definite increase in rate of growth during the past year.

Menstruation began at fifteen years of age, has been regular and of a twenty-eight-day cycle and lasting three days. Occasionally dysmenorrhea was present. The last period began June 15, 1936, this being the first occasion on which she has ever missed a period.

The patient was married for five years. No previous pregnancies. Husband had a bilateral inguinal adenopathy four years ago. He has not consented to the performance of a Frei test upon himself. Apparently transmission of the virus to the patient occurred at this time, the husband being the source of the infection. For the past eight months she has had a vaginal discharge. Diarrhea has been present for the past two months with 4 to 5 loose stools daily, but without gross pus or blood.

Physical examination revealed a well-developed and nourished colored female not acutely ill. Blood pressure 120/80. Oral hygiene was very poor. The vulva pre-

Fig. 1.—Photograph of genitalia showing elephantiasis of left labium majus.

sented a large mass the size of a grapefruit involving the left labium majus. It was firm, not tender, and of a pinkish brown mottled color (Fig. 1). The cervix was short, soft, and discolored. The uterus was enlarged to the size of a two to three months' pregnancy, symmetrical and soft. The appendages were not identified. Rectal examination revealed an annular stricture, tender to pressure, and would not admit the tip of the examining finger when forced.

*Laboratory Findings.*—R.B.C., 3,400,000; Hg, 11 gm. per cent; W.B.C., 8,600. Differential: Filamented polymorphonuclears 63 per cent, nonfilamented polymorphonuclears 10 per cent, lymphocytes 25 per cent, large mononuclears 2 per cent; blood Kahn negative. Urine negative. Aschheim-Zondek positive. Frei test 2-, 3-, and 4-plus using seven different antigens. Sedimentation time 30 mm./10 minutes. Blood chemistry: Total protein 9.9 gm. per 100 c.c. plasma; albumin 2.9 gm., globulin 6.5 gm., fibrinogen 0.5 gm., nonprotein nitrogen 17 gm.

*Pathologic Report.*—(Fig. 2.) A biopsy was taken from the tumor of the labium majus. The section is covered by squamous epithelium which was pigmented, thickened, and slightly edematous. The stroma was markedly thickened, edematous, and consisted of dense fibrous tissue. Numerous dilated lymphatics and thickened blood vessels surrounded by focal collections of lymphocytes and plasma cells were present.

*Course in Hospital.*—During the eleven-day period of observation in the hospital, the patient ran a rather uneventful course. Temperature, pulse, and respirations were normal. However, the diarrhea persisted, the patient having 2 to 5 loose stools daily. She was discharged to the Obstetrical Clinic on Sept. 9, 1936. Since the submission of this paper the patient has delivered a normal child. She is now receiving antisyphilitic treatment without any amelioration of the local findings. The child has been tested with six different known Frei antigens at various times with negative results. This is contrary to European findings.

Fig. 2.

Fig. 3.

Fig. 2.—Biopsy of lesion on left labium majus showing edema, fibrosis and perivascular round cell infiltration. ×70.

Fig. 3.—A portion of section shown in Fig. 2, demonstrating the same findings under higher magnification. ×200.

## DISCUSSION

Notwithstanding the syphilitic background, we feel that the virus of lymphopathia venerea and not the *Treponema pallidum* is the etiologic agent in the elephantiasis of the vulva and the stricture of the rectum. The simultaneous occurrence of syphilis and lymphopathia venerea is a common finding as first pointed out by Coutts and Bianchi,[7] moreover these clinical conditions commonly occur in nonsyphilitic patients and do not occur in syphilitic patients unless the Frei test is positive. The development of the lesions during the period of antisyphilitic treatment and the negative Wassermann reaction also favor the same etiology. The history of inguinal lymphadenitis in the husband preceding the development of the lesions in our patient suggests the source of the infection.

The positive results obtained with seven different Frei antigens is conclusive proof that the lesions are due to lymphopathia venerea. It is generally accepted that a positive Frei reaction with a reliable antigen and proper interpretation is as specific as any immunologic test in the realm of medicine. Bacon[8] after reviewing the literature on Frei reactions concludes that it is 96.7 per cent diagnostic. We have obtained a positive Frei reaction twenty-four years after the occurrence of bilateral inguinal adenitis. Our antigen is made either from pus or from infected tissue. The original technic of Frei is followed with the exception that the antigen made from infected tissue is allowed to remain in the ice box for several weeks before it is used. Experience has taught that the antigen is not active before this period of time, probably due to absorption of the virus by the tissue. As our criteria of strength of reaction we have followed the classification of Strauss and Howard[9] except that we have added a fourth class, i.e., four-plus, when the reaction proceeds to necrosis. Readings are made at the end of forty-eight and ninety-six hours, using a micrometer rule for measuring the actual depth and size of the reaction.

The close association of rectal stricture with lymphopathia venerea has been so often and thoroughly commented upon that further discussion is unnecessary.

Esthiomene is the less common clinical manifestation of the disease. The type of lesion depends upon the direction of lymphatic drainage from the site of the initial lesion. Drainage to the inguinal glands results in esthiomene, while drainage to the glands of Gerota results in rectal stricture. The generally accepted concept of the pathologic basis of esthiomene is lymph stasis following lymphatic obstruction, but Dorne and Zakon[10] incriminate the action of the virus on the affected tissues. They also maintain that the virus is active even in the tertiary stage of the disease.

The effect of the virus on fecundity and pregnancy has received but scant attention by workers in this field. Dick[11] states that women in the later stages of lymphopathia venerea are usually sterile. The exact mechanism by which sterility is brought about is apparently not definitely known. Some investigators maintain that the virus acts upon the entire generative system, but substantiating proof in the form of gross or microscopic studies is not offered.

Williams and Gutman[12] have recently called attention to two laboratory findings which may have differential value. They found that there is a rapid sedimentation time of the erythrocytes and a reversal of the normal albumin-globulin ration in the blood serum. In the above case the reversal was almost 2½ to 1, and it is to be noted there was no edema. We have found in a series of cases to be published later that the above phenomena occur in practically all patients. We have found the fibrinogen content of the blood serum to be uniformly normal, thus confirming the findings of Williams and Gutman. The exact mechanism of these chemical changes is not definitely known, but these workers attribute them to the same factors operative in other chronic infections such as kala-azar and leprosy, and in certain neoplastic diseases such as multiple myeloma.

## SUMMARY

1. The first proved case of lymphopathia venerea with esthiomene associated with pregnancy is presented.

2. The patient presented rectal stricture and esthiomene, the usual manifestations of this disease.

3. The Frei test was positive, and reversal of the albumin-globulin ratio and rapid sedimentation rate, both constant findings in lymphopathia venerea, were present in this case.

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# DYSTOCIA DUE TO FETAL TERATOMA

JULIUS KURZROCK, M.D., AND NORMAN PLESHETTE, M.D.,
NEW YORK, N. Y.

*(From the Department of Obstetrics of the Harlem Hospital)*

A LESS commonly encountered cause of dystocia is that due to fetal sacral teratoma. The standard texts mention this congenital anomaly as a potential cause of obstruction but give little or no space to its discussion. DeLee (sixth edition)[1] does not refer to it. Davis[2] mentions it briefly. Williams[3] states, "exceptionally, teratomatous tumors about the perineum and sacrum may offer a serious obstacle." Curtis[4] quoting Piper says, "cystic tumors should be punctured—solid tumors call for version or embryotomy."

A review of the literature discloses occasional reporting. Saxtorph,[5] 1775, and Veling,[6] 1846, report individual cases. In 1867 the first comprehensive review was done by Molk who reported 107 cases. Coudère[7] in 1890 reviewed 29 cases. Hohl collected 40 cases; Brown, 79 cases. In the past twenty years only isolated cases have been reported: Spitzer[8] in 1933; Kovats[9] 1934; Brenner[10] 1935.

The etiology of sacral teratoma is not known, but the blastomere theory of Bonnet, Marchand, and Robert Meyer is the most acceptable one.

The incidence of this tumor as reported by Colbert in 1893 was 1 in 34,082 births; Spitzer in 1932 reported 1 case in 20,042 births. There are no quoted figures as to the incidence causing dystocia, but they are undoubtedly much higher.

In all the reported cases this tumor was never diagnosed antepartum. There have been observed two concomitant findings. The majority of cases have an accompanying hydramnios and by far a great number have premature labors. The size of the mass per se does not inconvenience the patient.

The presentation is preponderantly by the vertex. In Molk's series of 107 cases 100 per cent were vertex. Coudère reports 25 vertex, 3 shoulder, and 1 breech presentation.

The labor records of these cases are for the most part facsimiles of one another. The usual story is that of a normal progressing labor. The head is delivered, but it is during the delivery of the trunk that the obstruction occurs. After vain attempts at extraction have failed, the possibility of this complication is considered and is usually verified by whole hand vaginal examination. A mass is felt impacted in the superior strait.

The treatment varies with the type of teratoma present. The cystic ones can be ruptured, thus relieving the obstruction. The solid tumors cause more trouble. Some

authors recommend the use of Siebold scissors to amputate the teratoma at its base and then remove the tumor by morcellation. Hirst recommends version or embryotomy.

The prognosis for the baby is usually hopeless; by far most are lost during delivery, the remainder die within a short time after delivery. The mother's prognosis is good.

M. L., a Porto Rican, thirty-eight years old, was admitted to Harlem Hospital Oct. 17, 1935. Menstruation normal, last period in January, 1935, due October, 1935. Obstetric history, gravida v, para iv. All previous deliveries were normal. The babies weighed between 7 and 8 pounds.

The patient registered in the out-patient department when she was six months pregnant, and her physical examination at this time was negative. Pelvic measurements were normal. The Wassermann was negative. When patient returned the following month, there were no abnormal findings. This was her last visit until admission to the hospital two months later.

On Oct. 17, 1935, in the morning, the membranes ruptured. She had no pains and remained at home doing her housework. At 6:30 P.M. of the same day she had one

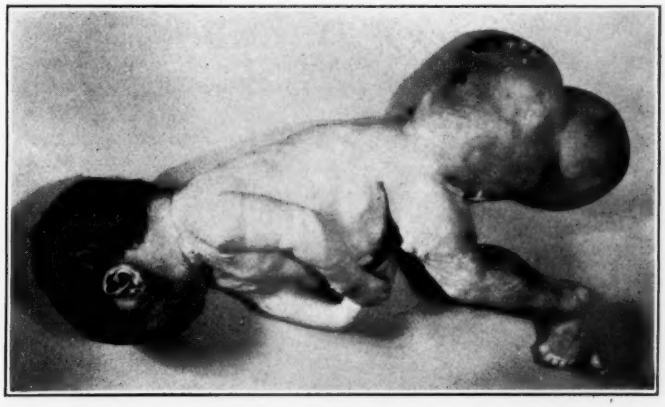

Fig. 1.

sudden, severe pain and expelled the fetus up to the umbilicus where it became impacted. She claims the baby died after making two voluntary movements. A physician was called but his attempts at delivery were futile. One hour later the patient was admitted to the Harlem Hospital. She was in good condition; temperature 99°, pulse 96, respiration 20, and blood pressure 120/70. The uterus, which was soft, not tender, and freely movable, was at the level of the umbilicus. No fetal parts were felt, and no fetal heart was heard.

Vaginal examination revealed a partially delivered dead baby from vertex to umbilicus. Under ether anesthesia it was found that the cervix was fully dilated. At the level of the fetal sacrum a large partly cystic and partly solid mass which was obstructing the delivery could be felt. The cystic mass was perforated and about 4 ounces of clear yellow fluid was expressed. It was then possible to deliver both feet, traction downward resulting in the expulsion of a large loculated mass attached to the sacrum of the baby.

The placenta and membranes were expressed completely, causing but slight hemorrhage. The perineum was intact, and the patient left the table in good condition.

She left the hospital on her sixth day against our advice. Up to this time she had an uneventful postpartum course.

*Pathologic Report:* The full-term female fetus with a crown-heel measurement of 50 cm. had normal head, trunk and extremities. Protruding from the perineal region between the rectum and coccyx was a globular mass measuring 16 cm. in diameter, entirely covered by skin. The rectum was present as a dilated orifice on the anterior surface. Some portions of the mass were cystic and others solid, the cystic portions containing clear, serous, straw-colored fluid and being lined with smooth, glistening membrane. The solid portion consisted of lobulated, soft, pinkish gray tissue which was somewhat friable and containing small spicules of calcium.

All internal organs were normal. The lungs were atelectatic except along the anterior margins where they were pink and containing air.

*Microscopic Diagnosis.*—Sections through various parts of the tumor showed many types of embryonal and adult tissue. Some postmortem degeneration was evident. The stroma consisted chiefly of a mesenchymatous myxoid tissue, with cell outlines indistinct, nuclei vesicular and ovoid or round. The stroma was very delicate and stained only faintly with eosin. There were masses of adult hyaline cartilage surrounded by an active perichondrium imbedded in the stroma. There were also many glandlike cystic dilatations lined by various types of epithelium, some columnar, some stratified squamous, some pseudostratified and others undifferentiated embryonal epithelial. However, there was no break in the basement membranes, and in any one gland the epithelium was regular and uniform. Some of the cysts contained coagulated fluid. There were also some collections of undifferentiated small round cells with hyperchromatic nuclei, which seemed to show occasional mitotic figures although it was difficult to make this out with certainty.

*Microscopic Diagnosis.*—Teratoma.

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## MELANOMA OF THE FEMALE URETHRA

Q. U. Newell, M.D., F.A.C.S., and W. C. Scrivner, M.D., St. Louis, Mo.

*(From the Department of Obstetrics and Gynecology, Washington University Medical School and Barnes Hospital)*

MELANOMA is a highly malignant pigmented tumor, commonly described as arising from a pigmented nevus of the skin. Melanoma of the vulva, clitoris, rectum, adrenal and other parts of the body have been reported. Melanoma of the external orifice of the female urethra is a most unusual rarity, hence we feel a report of this case is indicated.

### CASE REPORT

A white female, aged sixty-four years. Moderately obese with no complaints or symptoms except the pressure of a tumor near the urethra which troubled her when walking. Self inspection revealed a growth at the urethral opening.

Her family and past history were irrelevant. She had an uneventful menopause ten years ago. General physical examination revealed the patient to be in good condition for her age.

In February, 1932, a mass thought to be an innocent caruncle was excised from the urethra. This reappeared in November, 1932, with a different morphology and was removed (Fig. 1). Grossly the tissue appeared brownish black in color, vascular, and spongy in consistency. The pathologic report read: "The pigment is yellowish brown and is found between the cells. Some of it, however, is being taken up by phagocytic cells. The stroma is fairly dense with a definite tendency for the arrangement of the cells in nests."

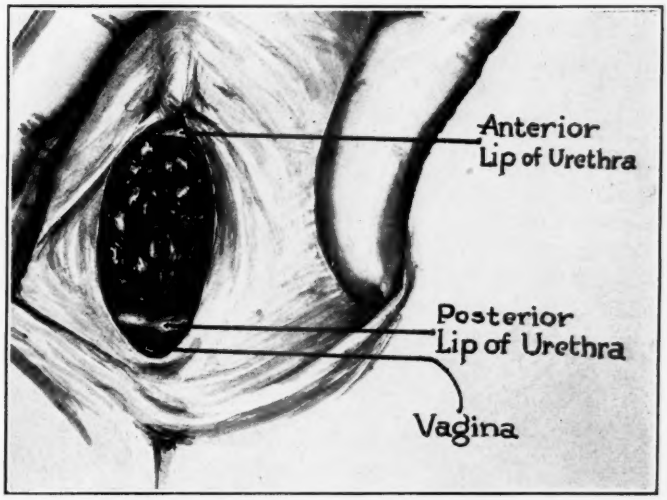


Fig. 1.—A drawing showing the growth of the urethra. The lips of the vulva are separated exposing the melanoma.

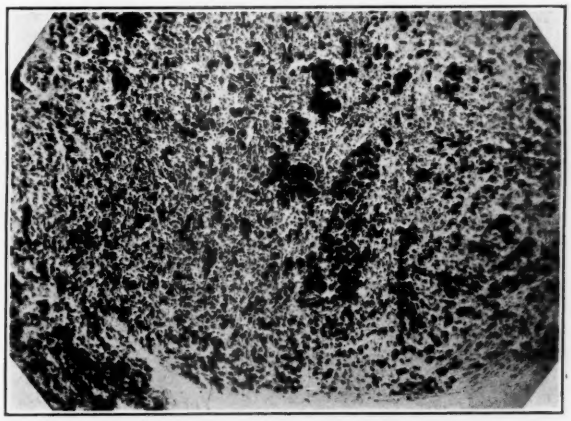

Fig. 2.—A low power photomicrograph of a section of the tumor. Note the large amount of pigment present.

*Diagnosis.*—Melanoma (Fig. 2). This growth was removed ten times and it always rapidly recurred, regardless of what form of treatment was given. It was cauterized with the actual cautery five times, using "cherry" heat. It was radiated four times with radium, by implanting 50 mg. of radium directly into the urethra for eight hours each time, and on one occasion deep x-ray therapy (200 K.V.) was given. The condition always showed improvement after radiation but within two to three months the growth would be as large and as ugly as before treatment.

In June, 1935, the growth began to spread very rapidly and the patient went to bed where she remained until her death, June 25, 1935. At the time of her death the melanoma had covered the entire vulva and vagina. The inguinal lymph nodes on both sides were involved and broken down, discharging a very fetid, reddish fluid. The cause of death was septicemia from the marked involvement of the growth. There was no clinical evidence of metastasis to liver, lungs, brain, or other vital organs. Unfortunately an autopsy could not be obtained.

## DISCUSSION

In searching the literature very carefully we are able to find only six other cases of melanoma of the female urethra reported, those by Reed,[1] Küstner,[2] Sänger,[3] Koerner,[4] Rosenthal,[5] Auer.[6] There is a difference of opinion as to the pathology of this malignant growth. Some authors contend that it is a melanosarcoma, others claim it is a melanocarcinoma. Graves,[7] Braasch,[8] Koerner,[4] Taussig,[9] Ewing[10] and others agree that the sarcomatous or carcinomatous nature of the lesion is usually a very difficult decision to make. However, Broders[11] claims the proper classification is one of melano-epithelioma. Frequently the diagnosis is made with reservations. This is well understood when we consider how variable these lessions may appear histologically. Along with melanoblastomas of the vulva in general, these tumors contain a pigment varying in shades of black or blue. They tend to spread by lobes or knots or more extensively through superficial lymphatics. Sometimes, as in this case, the transportation of pigment can be demonstrated.

Frequently the local lesion tends to heal without delay after excision, only to have hopes banished by fatal metastasis elsewhere. Peculiarly true is the lack of local symptoms accompanying most of these lesions.

## TREATMENT

The variable nature together with abundant properties of malignancy renders these tumors unalterable to x-rays, radiation or surgery with any degree of success. Nowhere does one find encouraging suggestions of therapy for the case at hand. Surgery is definitely limited because of the anatomical relationships which must not be disturbed for practical or esthetic reasons.

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105 Lister Building.

# GONOCOCCIC PERITONITIS IN PREPUBESCENT FEMALES

BERNARD NOTES, M.D., F.A.C.S., WASHINGTON, D. C.

*(From the Department of Obstetrics and Gynecology, George Washington University School of Medicine.)*

CONTRARY to recorded opinion, gonococcic peritonitis in prepubescent females is not rare. I am able to report 16 cases which have occurred during the past two years. A thorough search of the literature reveals but 55 reported cases,[1] which together with mine make a total of 71. The reason for this report is to point out the frequency with which gonococcic peritonitis occurs in immature females, since in the past I have seen a number of cases diagnosed appendicitis or explored to rule out appendicitis.

Holt and McIntosh[2] point out that this disease is seen in children but not in infants. This is true for the reason that the cervix acts as a barrier. The cervix is seldom infected in children under 6, prepubescent development of its epithelium not yet having been attained. However, it can and does occur in young children since 2 of our 16 patients were four years of age. Our oldest was ten, and none had reached puberty. All were proved by positive smears and had the characteristic clinical finding in the lower genital tract, polypoid urethritis. Symptoms of peritonitis were usually present for forty-eight hours, and tenderness was localized deeply in both lower abdominal quadrants, rigidity was moderate and could be overcome by steady gentle pressure, and vomiting was absent. Average highest temperature and leucocyte count during the acute phase was 102.8° F. and 22,679, respectively. All subsided in a few days with cleansing intravaginal douches. After localization in the fountain-head focus, the cervix, electrocauterization was performed with excellent results.[3] None suffered exploratory laparotomy.

## CONCLUSIONS

1. Gonococcic peritonitis is occasionally seen in prepubescent females and should be borne in mind when considering differential diagnosis of acute abdominal conditions.

2. Treatment, during the acute phase, is supportive and exploration should be performed only after due consideration. Electrocauterization of the cervix, during the chronic phase, gives the best assurance of cure.

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1801 EYE STREET, N. W.

# Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

## REVISION OF BIRTH, DEATH, AND STILLBIRTH CERTIFICATES

A BRIEF REPORT BY THE SUBCOMMITTEE ON CAUSES OF MATERNAL, FETAL, AND NEONATAL DEATH OF THE AMERICAN COMMITTEE ON MATERNAL WELFARE*

IN APRIL, 1937, the American Committee on Maternal Welfare appointed a subcommittee (1) to consider the causes of maternal, fetal, and neonatal mortality in relation to the forthcoming revision of the International List of Causes of Death, the rules of procedure for assigning cause, the revision of the birth and death certificates; and (2) to make suggestions directed toward securing information on a nationwide scale prerequisite for planning an effective program for the reduction of mortality from these causes.

The subcommittee calls attention to the magnitude of the loss of life from these causes and conditions, practically all of which are connected with pregnancy and childbirth. The total loss from these causes in the United States amounts to more than 150,000 lives each year. The total loss in 1935, as shown by the Bureau of the Census figures, was 161,249 lives, including 14,296 maternal deaths (12,544 deaths assigned to pregnancy and childbirth and 1,752 deaths in which pregnancy or childbirth was a complicating factor), 77,119 stillbirths, and 69,834 infant deaths in the first month of life, of which 56,262 were due to prenatal and natal conditions.

The total loss arising from these causes connected with pregnancy and childbirth is, however, far greater than is indicated by the information obtained from the registration of births and deaths. Many maternal deaths following early abortion probably go unregistered as such. The registration of stillbirths is generally recognized as incomplete. Many mothers who survive childbirth do so with impaired health.

With the continuing decline in the birth rate it becomes imperative to develop statistics prerequisite for planning an effective program for the reduction of mortality due to conditions of pregnancy and childbirth. The loss of life in the United States as shown by the maternal mortality rate is high and has not been markedly reduced during the period of record (1915-35). Our neonatal mortality and stillbirth rates also continue high and fail to show marked reduction. Before we can hope for effective reduction of these losses, accurate nationwide information, which will reveal the conditions underlying this mortality, must be made available. This information is within the possibility of collection through the regular channels of birth and death certification. The certificate forms and the statistical procedures must be revised to provide the prerequisite information.

*This report was accepted and approved by the American Committee on Maternal Welfare, Sept. 21, 1937.

### A. REVISION OF THE STANDARD BIRTH CERTIFICATE

The subcommittee points out the great need for medical information with respect to all births (live and still). For the reduction of mortality connected with birth, accurate information must be made available with respect to prenatal and natal conditions. This information is prerequisite, not only for the reduction of fetal and infant deaths, but also for the reduction of maternal deaths and for the improvement of maternal and child health.

The subcommittee recommends that the standard birth certificate used for registration of both live and stillbirths be revised to include the following information:

1. Evidence of life at birth, i.e., breathing, movement of voluntary muscle, heart beat; or no evidence. (To be used for statistical purposes in classifying the birth as live or still.)
2. Period of gestation at delivery in terms of weeks.
3. Week of gestation in which mother first came under supervision of attendant at birth.
4. Complications of pregnancy.
5. Complications of labor, including statement as to whether delivery was natural or operative, and if operative the name of the operation.
6. Physical defects in the child at birth, especially defects which are or may result in crippling.
7. Time of fetal death with respect to labor. If the delivery was operative, the time of fetal death with respect to operation. (Applicable for stillbirths only.)

The subcommittee recommends that the definitions of stillbirth and live birth, as incorporated in the Rules of Statistical Practice of the American Public Health Association, appear on the reverse side of the standard birth certificate.

### B. REVISION OF THE RULE WITH RESPECT TO MENTION OF CHILDBIRTH ON DEATH CERTIFICATES

The subcommittee considers that the present instruction with respect to mention of childbirth on death certificates is inadequate to cover deaths associated with puerperal causes. The instruction as now stated in notes to the International List of Causes of Death, 1929 revision, page 15, and in the Physicians' Pocket Reference, 1931 edition, page 15, reads:

"Whenever parturition or miscarriage has occurred within 1 month before the death of the patient, the fact should be certified, even though the childbirth may not have contributed to the fatal issue."

This instruction should be revised to read:

"Certification must be made for all deaths of females 15 to 49 years of age as to whether the patient was known to have been pregnant or to have been delivered of any product of conception within the 3 months prior to death."

### C. REVISION OF STANDARD DEATH CERTIFICATE

The subcommittee recommends that special items be incorporated in the standard death certificate applicable for all deaths in the first month of life and all deaths of women associated with pregnancy and childbirth. It recommends the inclusion of one question on the face of the certificate applicable for all deaths of females fifteen to forty-nine years of age:

"Was this female pregnant or delivered of any product of conception within the three months prior to her death?"

It recommends that questions adapted to obtaining the following information regarding conditions associated with pregnancy and childbirth be shown on the reverse side of the certificate:

1. *For Deaths in Which Pregnancy or Childbirth Occurred Within Three Months Prior to Death.*—(a) Was woman delivered or did death occur before delivery? (b) Period of gestation in terms of weeks? (c) If delivered, was child born alive or dead? (d) Week of gestation in which woman came under supervision of attendant at death? (e) Complications of pregnancy? (f) Complications of labor and delivery? (g) Postpartum complications? (h) Number of days between delivery and death of mother?

2. *For Deaths in the First Month of Life.*—(a) Weeks of gestation at birth? (b) Complications of pregnancy? (c) Complications of labor and delivery? (d) Physical defects in child at birth? (e) Postnatal conditions which contributed to death?

### D. CAUSES OF MATERNAL DEATH DIRECTLY DUE TO PREGNANCY, LABOR, AND PUERPERIUM

The subcommittee has considered the causes of death as listed in the 1929 International List of Causes of Death and the Manual of Joint Causes (1933) as directly due to the puerperal state. It finds: (1) That certain types of causes fundamentally puerperal in nature fail to be included in Group XI, Diseases of Pregnancy, Childbirth and the Puerperal State; (2) that the cause classification for Group XI does not afford information showing the fundamental causes of maternal death; and (3) that many terms now accepted as indicating the cause of maternal death fail entirely, when mentioned alone, to give an accurate description of the cause of death. This section of the report covers these three aspects of mortality due to pregnancy, labor, and the puerperium.

1. *Types of Causes to be Included in Maternal Deaths.*—The subcommittee at this time limits its recommendations with respect to additional diseases and conditions to be considered as directly due to pregnancy, labor, and the puerperium to deaths of the following types: (a) Maternal deaths with mention of chronic nephritis (about 228 maternal deaths certified with mention of chronic nephritis were assigned to chronic nephritis in 1935). (b) Maternal deaths now assigned to violence and accidents, which include criminal abortions (259 deaths certified in these terms were assigned to violence and accidents in 1935).

2. *Cause Classification for Maternal Deaths Due to Diseases and Conditions of Pregnancy, Labor, and the Puerperium.*—The subcommittee points out that there are only four fundamental causes of maternal death—infection, toxemia, hemorrhage, and trauma. It recognizes that deaths prior to the 28th week of gestation (the period of previability) in general constitute a maternal and fetal problem separate and distinct from deaths that occur from the 28th week onward (the period of viability).

The general plan recommended for assigning cause of death under this classification[1] is that infection should invariably take precedence over every other puerperal disease or condition with which it was simultaneously mentioned. Hemorrhage should take general precedence over other puerperal diseases or conditions with the exception of infection. Toxemia should take general precedence over other puerperal diseases or conditions with the exception of infection or hemorrhage.

3. *Undesirable, Nonacceptable Terms for Certifying Cause of Maternal Death.*—The subcommittee presents a list of terms undesirable and nonacceptable for certifying cause of maternal death (Appendix I). The terms recommended to be considered

[1]The full report of the subcommittee included a list of causes of maternal death recommended for consideration in connection with the 1938 revision of the International List of Causes of Death. The recommended list has been favorably considered by the Committee on Accuracy of Certified Causes of Death of the American Public Health Association and the U. S. Bureau of the Census.

as undesirable and nonacceptable for certification are those which fail entirely, when mentioned alone, to give definite information with respect to the cause of maternal death. The subcommittee recommends that this list of undesirable terms be added to those set forth in the 1929 revision of the International List of Causes of Death, and that whenever a death is certified as due to any of these undesirable terms the local registrar should require an explicit statement from the reporting physician as to the cause of death, the explicit statement to be expressed in so far as possible in terms which are "approved" or recommended for use.

In making this recommendation the subcommittee is cognizant of the work entailed upon both registration officials and physicians in connection with obtaining satisfactory information regarding cause of death. It points out that accurate statistics with respect to the cause of maternal death are the first prerequisite for planning an effective program for the reduction of maternal losses. It believes that the usefulness of the statistics may be greatly enlarged through the cordial cooperation of the medical profession and the registration officials.

### E. SUPPLEMENTARY TABULATIONS BY THE BUREAU OF THE CENSUS

1. *Deaths Associated With Pregnancy and Childbirth.*—The subcommittee calls attention to the great need for information on maternal deaths associated with pregnancy and childbirth and to the fact that no published statistics are available for the United States later than for the year 1925. Several foreign countries have published such statistics much more recently than the United States; the majority of these countries published the statistics annually.

It is recommended that the United States Bureau of the Census tabulate and publish annually statistics showing the total number of deaths in which pregnancy and childbirth are mentioned on the death certificate, by primary and principal contributory cause of death, and the puerperal condition mentioned on the certificate for deaths in which the puerperal state is mentioned but is not considered either a primary or a principal contributory cause.

2. *Deaths in the First Month of Life.*—The subcommittee calls attention to the fact that there are unquestionably many more deaths in the first month of life due to prenatal and natal conditions than can be classified as such from the statistics made available in "Birth, Stillbirth, and Infant Mortality Statistics," where the short list of causes is used. The figures in "Mortality Statistics," where the detailed International List of causes is used, show that many deaths grouped together under "All Other Causes" in the short list are essentially due to prenatal and natal causes which are operative in the first month, notably diseases of the thymus, hemorrhagic conditions, and cerebral hemorrhage.

The subcommittee recommends that the United States Bureau of the Census issue an annual tabulation of deaths under 1 month, showing detailed information for each cause title of the International List similar to that now shown in "Mortality Statistics" for deaths under 1 year and for deaths at older ages. This recommendation is not to be interpreted as suggesting that the subcommittee is not cognizant of the objections to the present list and not desirous of securing at the earliest possible date a revision of the list of causes of death applicable to the first month of life. This information on cause, as tabulated under the 1929 revision of the International List, is needed for the work on the revision of causes of neonatal death.

### F. WORK IN PROGRESS

The conclusions and recommendations offered by the subcommittee at this time cover only a few of the major aspects of the work with which it is charged.

No recommendations are presented at this time with respect to the precedence to be given in instances where two or more conditions are certified simultaneously. The subcommittee recognizes the importance of such recommendations and anticipates giving thorough review to methods of assignment procedure as soon as the necessary statistical information is made available for its use.

No recommendations are presented with respect to the classification of causes of stillbirth. The subcommittee is interested in securing the findings of the special study, Causes of Stillbirth, being made by the Children's Bureau with the cooperation of the Subcommittee on Stillbirths of the American Public Health Association which includes 6,750 schedules supplied by 229 hospitals located in 25 States and the District of Columbia, and also the findings from other special studies being made in several sections of the country.

No recommendations are presented at this time with respect to the classification of causes of infant death due to prenatal and natal conditions. The cooperation of the obstetric and pediatric societies will be sought.

The future work of this subcommittee will include consideration of (1) rules of procedure for assigning cause of maternal death; (2) classification of cause and rules of procedure for assigning cause of stillbirth; (3) classification of cause and rules of procedure for assigning cause of infant death due to prenatal and natal conditions which occur mainly in the first month of life.

ROBERT L. DENORMANDIE, M.D., *Chairman*
GEORGE W. KOSMAK, M.D.
PHILIP F. WILLIAMS, M.D.
ELIZABETH C. TANDY, SC.D.

## APPENDIX I

*List of Undesirable, Nonacceptable Terms for Certifying Cause of Maternal Death*

Abnormal labor
Abnormal parturition
Abortion
Accident of labor
Accident of pregnancy
Accidental abortion
Accouchement
Application of forceps
Atony of uterus during parturition
Breech presentation
Cephalotomy
Cephalotripsy
Cesarean operation
Childbed
Childbirth
Confinement
Consequence of labor (mother)
Craniotomy
Criminal abortion (mother)
Cyesis
Dead fetus in uterus
Deformed pelvis (female 15-44 years)
Delayed delivery
Difficult labor
Disease of placenta
Displacement of pregnant uterus
Dropsy of amnion
Dystocia
Embryotomy
Evacuation of uterus
Faulty presentation (mother)
Fissure of nipple, puerperium
Fistula of breast, puerperal or unqualified
Following childbirth
Foot presentation
Forced delivery
Forceps operation
Galactocele
Galactorrhea
Gestation
Hebotomy
Hydramnios (mother)
Hydrops amnii
Hydrorrhea gravidarum
Hydrorrhea in pregnancy
Hysteralgia of pregnant uterus
Immature birth
Immaturity
Induced abortion

Induced premature labor
Inertia of uterus
Instrumental delivery
Intentional abortion
Labor (unqualified)
Laparoelytrotomy
Malpresentation
Mammary fistula
Menstruation during pregnancy
Miscarriage
Missed abortion
Missed labor
Multiple birth
Multiple parturition
Multiple pregnancy
Neuralgia of pregnant uterus
Obstetric operation
Overdistention of uterus
Parturition
Perineorrhaphy
Porro operation
Pregnancy
Pregnancy in abnormally formed uterus
Premature birth
Premature delivery
Prolapse of pregnant uterus
Prolonged labor
Protracted labor
Puerperal accident
Puerperal apoplexy
Puerperal disease of breast
Puerperal fissure of nipple
Puerperal fistula of breast
Puerperal displacement of uterus
Puerperal fistula of mammary gland
Puerperal galactophoritis
Puerperal state
Puerperium
Result of labor (without further explanation)
Retarded labor
Retention of dead ovum
Retroversion of pregnant uterus
Spontaneous abortion
Spurious labor pains
Subinvolution of uterus
Symphyseotomy
Transverse presentation
Version during labor

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**Cotte, G.: What Place Have Autogenous Ovarian Grafts in Gynecologic Therapy,** Gynécologie **35**: 641, 1936.

Cotte is firmly convinced of the value of autogenous ovarian grafts. The two chief indications for this procedure are sterility and prevention of menopausal symptoms. To overcome sterility, an ovary may be transplanted into the uterine cavity or in the uterine cornua. Ovarian grafts may also be used to conserve menstruation or to prevent disturbances of the climacteric following castration. The author is of the opinion that a castrated woman is not a normal individual. He also believes that in spite of the recent advances in endocrinology, we cannot prevent or overcome the disturbances which follow castration. Hence in such cases ovarian grafts have their most important indications.

In cases of salpingitis Cotte prefers to leave the uterus, because he believes that persistence of menstruation is the best guaranty for continued function of the ovaries. Leaving the uterus, therefore, is a far better procedure than performing subtotal hysterectomy and grafting an ovary under the skin.

J. P. GREENHILL.

**Zappi, F., and Costanzo, E.: Severe Hemorrhage Due to Rupture of the Hymen Following Coitus,** Clin. ostet. **15**: 9, 1937.

The author reports the case of a very severe hemorrhage following defloration of the hymen and briefly comments on the mechanism, the diagnosis, and the cure of such an infrequent lesion.

AUGUST F. DARO.

# Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

## Review of New Books

### Gynecology

The seventh volume of *Handbuch der speziellen pathologischen Anatomie und Histologie*[21] deals with diseases of the ovaries, written by John Miller of Wüppertal-Barmen. The previous installments, VII/1, dealt with the uterus and tubes, and VII/2 with the pelvic connective tissues and uterine ligaments. This concludes the female genital organs. The volume is of large size, 1,047 pages.

There are 5 main divisions, a short normal anatomy and physiology; the diseases of the ovary including inflammatory troubles and granulomatous involvements, and simple nonneoplastic cysts; neoplasms; parasites and foreign bodies; injuries of the ovary.

The anatomic description is very summary. Decidual reaction is considered entirely normal in pregnancy and independent of inflammatory irritation. The physiology although short, is up to date and informative. Malformation and deviations in form, size, and position are taken up. An excellent discussion of ovarian pregnancy is given. More space is devoted to tuberculosis of the ovary than to the other inflammatory infections.

A good classification of simple nonneoplastic cysts is offered. These are not considered retention cysts. Among them are included the lutein cystic formations. Endometriosis of the ovary with all the theories offered is well described.

A new classification of neoplasms is offered. There are 2 main divisions, (1) the ripe homeotypic, clinically benign, forms and (2) the unripe, heterotypic malignant forms. Each of these is subdivided into connective tissue, epithelial and teratoid growths. Endothelioma of the ovary is called a mere fiction. Pseudomucinous cystomas are classified under teratoid growths as first proposed by Bland Sutton in 1888.

Under Classification 1, namely homologous or homeotypic, neoplasms of epithelial derivation, the author places serous surface or ciliated tumors such as fibroadenoma and cystomas of the ovary, a classification which does not clarify the situation.

Particular emphasis is placed upon the newer subgroupings which are attracting much discussion in the literature at the moment. Of these, an excellent presentation of Brenner tumors, oophoromas, is given. Although Schiller's classification of basal cell carcinoma is fully concurred in by the author, he has not as yet separated this grouping; basocellular epitheliomas with granulosa cell tumors and basal cell carcinomas, clinically malignant, are still grouped together. The estrogenic potency and consequent physiologic effect upon the uterus of the granulosa cell tumors is well brought out. A detailed description of both seminoma and arrhenoblastoma are

[21] **Handbuch der speziellen pathologischen Anatomie und Histologie.** Siebenter Band: Dritter Teil: Die Krankheiten des Eierstockes. John Miller. Mit 145, zum Teile farbigen, Abbildungen, 1047 Seiten. Verlag von Julius Springer, Berlin, 1937.

offered. In all these new varieties of tumors dealt with, the illustrations are excellent and numerous; in contradistinction with this, the majority of the commoner forms of ovarian growths might well have received more illustrations.

It is impossible to give even an idea of the immense amount of material, well arranged, with comparatively easy reference to the literature contained in this volume. Both the clinical and pathologic aspects have been fully and adequately treated. The statistics of most of the types that have been fully accepted are mainly from the older literature, while the statistics dealing with the newer classifications are more recent. The reason for this is easily understandable. Both an authors and subject index conclude the volume. This publication will prove indispensable as a reference book for any one who desires to find the latest information and literature dealing with ovarian diseases.

*—R. T. Frank.*

This pamphlet, *Périodes de Fécondité et de Stérilité Chez la Femme,*[22] forms one of a series on research and application in medicine and surgery published by Masson. Here Vignes and Robey discuss whether there exists absolutely a period of fertility and a period of physiologic sterility according to the findings of Ogino and Knaus. This new method of contraception is formulated on three statements: the expelled ovum has a very limited life, the spermatozoa have a very limited life in the genital passage of a woman, the ovum is produed at a fixed date in the menstrual cycle. In a succeeding chapter they discuss the life of the ovum, the travels and survival of the spermatozoa.

The unusual length of time in which spermatozoa can be preserved in vitro is compared with their short life in the genital tract of the woman. In discussing the artificial preservation of spermatozoa they mention such factors as the rôle of pH, of the osmotic tension, and of the temperature, and contrast this with what is known of such findings in the female. They do not believe that the spermatozoa survive for a greater period of time than forty-eight hours, although they admit that it is possible that the duration of such life may be variable. They question whether spermatozoa, which appear to be alive on their recovery from the genital passage after a period of twenty-four hours, might be capable of fertilization. In the third chapter they discuss the known factors of ovulation and recount the exceptions which have been noted. The particulars of practical application of the method of Ogino-Knaus are given and are followed by various pertinent criticisms.

While the authors believe that the time of ovulation is a fixed point in the menstrual cycle of the woman, they conclude, however, that there are valid objections, and that there appear to be no criteria which permit one to say that a woman is either going to be normal or exceptional. An excellent bibliography on the subject is appended.

*—Philip F. Williams.*

Von Mikulicz-Radecki in a contribution read before the Koenigsberg Scientific Society, *Der Eiauffangmechanismus bei der Frau und seine Bedeutung für die Sterilität,*[23] discusses the probability of a protective mechanism whereby the ovum expelled from the ruptured follicle reaches the lumen of the tube. The various theories advanced to explain this migration are weighed. The physiology and anatomic relations at the time of ovulation in various animals are described.

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[22] **Périodes de Fécondité et de Stérilité Chez la Femme.** Par H. Vignes et M. Robey. 85 pages. Masson et Cie, Paris, 1936.

[23] **Der Eiauffangmechanismus bei der Frau und seine Bedeutung für die Sterilität.** Von Felix v. Mikulicz-Radecki, Max Niemeyer, Halle (Saale), 1937.

In the course of the many operations performed for sterilization, for feeble-mindedness and inheritable diseases, von Mikulicz-Radecki has had ample opportunity to observe the normal pelvic organs at various stages of the menstrual cycle. He found that about twelve days after the beginning of the menstrual cycle profound changes occurred in the relationship between the tube and ovary in that the tube, the fimbriated extremity and the mesosalpinx formed a barrier around the ovary. This cyclical anatomic finding he terms the "bursa-ovarica stellung," and finds that it almost completely shuts off the ovary from the peritoneal cavity. This predisposes to a rupture of the matured follicle into the lumen of the tube. This phenomena is discussed at length in its relation to the possible operative maneuvers suggested in the treatment of sterility. Where the tube cannot be freed to again perform this function he prefers cornual implantation of the ovary, with vascular pedicle, as originated by Estes.

*—Philip F. Williams.*

Vital statistics reveal as one of our social phenomena a continuous decline of the birth rate. As the author of *Childless: A Study of Its Causes and Treatment*[24] says: "From the first birth records (Sweden, 1750) to the present, each succeeding census in every part of the civilized world has shown a diminishing birth rate." As the curve downward became steeper a widespread interest has sprung up in the factors responsible for the falling birth rate. The modern study of sterility and its treatment really dates from the pioneer work of Hühner and Rubin and has been influenced by the stimulus of a coincident development in reproductive physiology.

To inform the public of the present status of our knowledge of sterility, Dr. Berkow presents this book. In the philosophic consideration of the underlying and historic phases of this problem, the author discusses the ancient beliefs and religious and legal aspects connected with sterility. He feels that contraception, which is the principal agent of the falling birth rate, plays a minor rôle in the production of childless marriages. The various theories, biologic predestination, the influence of civilization and other factors are assessed. The present nationalistic attitudes toward the problem are mentioned. The falling birth rate, the author says, is regarded as a national problem but the rising tide of sterility is still considered an individual one.

In the biologic aspects of reproduction he notes accurately the facts of conception and development and points them out. A discussion of the physiology of reproduction includes such topics as rhythm theory, development of abnormal body forms and the relationship of glandular influences and abnormalities of fertility. The chapter on the relationship of diet to fertility affords an opportunity for an explanation of the properties of the vitamins. The influence of congenital obstacles and gonococcal infections are clearly explained. There is a rational discussion of modern obstetrics in the chapter of one child sterility.

In the third part of the book the author rather briefly discusses the treatment of sterility. Fortunately he emphasizes the need and necessity for a prolonged study of both partners in a childless marriage. Again reverting to a philosophic attitude he answers with effectiveness how modern life can be reconciled with the question of sterility, and outlines the position of the state.

The pleasant manner in which the book is written and the easy style in which the medical problems are discussed make the book readily understandable by the general public.

*—Philip F. Williams.*

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[24]**Childless: A Study of Sterility, Its Causes and Treatment.** By Sam Gordon Berkow, M.D. Illustrated, 307 pages. Published by Lee Furman, Inc. 381 Fourth Ave., New York City, 1937.

*Carcinoma of the Female Genital Organs*[25] by Malinowsky and Quater was translated from the Russian by A. S. Schwartzmann. It is a monograph of 11 chapters written by 10 different Russian physicians. Just why this monograph was selected for translation is not apparent to me as it contains nothing either startlingly new in its observations or presentation.

As might be expected, when such a subject as the etiology of carcinoma is dealt with, this chapter boils down to the possible causes as chronic irritation and embryonal cells. Calcium intravenously is suggested for inoperable carcinoma. The concluding chapter deals with the disability produced by carcinoma of the female sex organs.

—*R. T. Frank.*

Crossen and Crossen's *Synopsis of Gynecology*,[26] second edition, is far superior to the usual run of synopses. A great deal of information is concisely and understandably presented. Both the physiology as well as the examination of the patient are of unusual excellence.

Exception may be taken to a number of the statements. For example, on page 80, "hypoactivity of the gonad causes a masculine shift in the female and a feminine shift in the male." On page 114 "pelvic massage and dilatation of the cervix, under antiseptic precautions, aid in promoting ovulation." In comparison with other chapters, that dealing with relaxation of the pelvic outlet is quite insufficient. In the discussion of dyspareunia, the important psychic factor is entirely omitted.

—*R. T. Frank.*

The second edition of Benthin's *Therapy of Women's Diseases*[27] appears four years after the first one. The chapter on endocrine disturbances has been rewritten and enlarged. The book is designed mainly for the general practitioner.

It is noticeable that the modes of therapy advised in many instances differ greatly from those practiced in this country. For puberty bleeding, in addition to hygienic measures, curettage is advised early. In very stubborn cases, and as rarely as possible, x-ray can be used. Among the treatments for amenorrhea, hot sitz baths, uterine diathermia, estrogenic hormones, and to my surprise, curettage are advocated. In stubborn cases, so-called "irritative dosage" of x-ray to the ovaries is suggested. In the treatment of sterility, mention is made of Fruktulet, small perforated aluminum cervical drains, to be worn for several days after which intrauterine treatment can be given, to minimize the resultant discharge. The book concludes with a formulary and additional hints for office practice.

—*R. T. Frank.*

## Endocrinology

*The Endocrines in Obstetrics and Gynecology*[28] by Kurzrok has been written by an experienced laboratory research worker who has contributed substantially to research and who likewise has a large clinical experience. It is therefore a work of importance.

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[25]**Carcinoma of the Female Genital Organs.** By M. C. Malinowsky and E. Quater. Translated from the Russian by A. S. Schwartzmann, M.D. Illustrated, 255 pages. Published by Bruce Humphries, Inc., 306 Stuart Street, Boston, Mass.

[26]**Synopsis of Gynecology.** By Harry Sturgeon Crossen, Professor Emeritus of Clinical Gynecology, Washington University School of Medicine, etc. and Robert James Crossen, Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Second edition. With 106 illustrations, 247 pages. The C. V. Mosby Company, St. Louis, 1937.

[27]**Therapie der Frauenkrankheiten.** Von Professor Dr. W. Benthin. Koenigsberg i.P. Zweite, neubearbeitete Auflage. Mit 23 Abbildungen im Text, 210 Seiten. Urban & Schwarzenberg, Berlin und Wien, 1937.

[28]**The Endocrines in Obstetrics and Gynecology.** By Raphael Kurzrok, Ph.D., M.D., Associate in Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University. Illustrated, 488 pages. Williams and Wilkins Company, Baltimore, 1937.

There are short concise introductory chapters on the history of endocrinology, embryology, etc. One hundred and eighty pages are devoted to a description of the various glands of internal secretion. These all are ample, clear, and up-to-date, based on careful utilization of the literature. The chapter on the physiology of estrone is particularly good. An excellent chapter on the chemistry of the sex hormones follows. As is to be expected in a developing branch of medicine, many of the subjects dealt with, permit of various interpretations. However, when the author speaks of a brain sex center and of a bleeding hormone, it should have been emphasized that these two concepts are largely hypothetical and illustrate personal views. Kurzrok accepts as definitely proved that the follicle-stimulating and luteinizing hormone of the anterior pituitary are separate entities.

A large portion of the book is devoted to the application of endocrinologic knowledge to the treatment of gynecologic and obstetric disturbances. It may be stated that the author is a very active and optimistic therapeutist. On the other hand his description of the syndromes is clear, understandable and accurate. The text is illustrated by excellent figures and by accurate case histories which show a thorough workup of the patients. To a reader familiar with the personal factors which still must so largely enter into the interpretation of diagnosis and therapy in endocrinology, this book should prove of utmost value. The general practitioner may find the methods advocated less effective than anticipated, when applied. Each chapter has a valuable bibliography which will prove of equal use to both the laboratory worker and the clinician. The book contains an immense amount of information otherwise to be obtained only by intensive and laborious delving into the literature, which has attained colossal proportions.

—*R. T. Frank.*

Fels' *Hormone of the Corpus Luteum*[29] is a monograph covering the biology, chemistry, and therapeutic application of this hormone. Fels has been a pioneer in this field and together with Slotta was one of the first to isolate and obtain this hormone in crystalline form. Much of his work was done in Breslau at the Klinik Fraenkel, and continued and completed at the Lying-In Institute of Buenos Aires. Consequently it is written from a personal standpoint and based upon personal investigation. Of the tests, he prefers the Corner to the Clauberg or Knaus test, although the Clauberg reaction is more delicate than the Corner method.

In these pages an excellent presentation of our knowledge of the subject will be found, with a very satisfactory exposition of the entire subject, including the literature.

The subjects covered are historical, introductory, the tests with their modifications, methods of standardizing the hormone, especially the biologic effects produced. Fels is convinced that the separation of the symphysis noted in the guinea pig is due to the estrogenic hormone. He likewise gives a full description of how the yellow body reacts on the hypophysis, the breasts, and nidation. The biologic relation between the estrogenic and corpus luteum hormone is discussed. That this hormone like the others is not species specific has been amply proved. It can be found only in the yellow body and the placenta, and has been demonstrated in the blood and urine although in very small concentration. The effect of the corpus luteum hormone on the male genital tract is also taken up. The excellent chapter on chemistry and synthesis of the hormone was written by Slotta (now in São Paulo, Brazil). The concluding chapter deals with the therapeutic application of progestin. This monograph is a valuable contribution.

—*R. T. Frank.*

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[29]**Das Hormon des Corpus Luteum.** Von Dr. Erich Fels, Instituto de Maternidad de la Sociedad de Beneficencia, Buenos Aires. Mit 40 abbildungen im text, 169 seiten. Franz Deuticke, Wien, 1937.

Kehrer has written a 564 page monograph on *Endocrinology and the Gynecologist.*[30] The title, however, might have been "The Causes of Amenorrhea." The author accepts prepuberal and postclimacteric amenorrhea, conditions of amenorrhea during which the ovarian function persists. He considers the cerebrum, the diencephalon, the uterus, and ovaries a biologic unit. A full and up-to-date analysis of the sites at which the various sex hormones originate and the tests for their demonstration is given. He accepts Seitz's classification of amenorrheas. An unusual casuistic, largely obtained from the literature, on anomalies, hermaphroditism, as well as on ovarian tumors some of which do and others which do not produce amenorrhea, is offered. Then come the endocrine syndromes in which amenorrhea is noted, including Froehlich's, Laurence-Moon-Biedl syndrome, lipodystrophy, acromegaly, brain tumors, etc.

An immense amount of material will be found in the pages of this monograph which is merely a source book covering a great deal of the literature. The value of this book is somewhat impaired by the incomplete bibliography, incomplete as to authors as well as to the sources of the references.

—*R. T. Frank.*

*The Rabbit Test*[31] by Anklesaria is a monograph dealing with this test for pregnancy. The first 30 pages are introductory and give an extensive review of the literature dealing with the physiology of the female sex organs, as well as the diagnosis of pregnancy by other methods. The remainder of the monograph describes the technics, the application of the test, and a considerable casuistic material in which the test proved of value. Special emphasis is laid in distinguishing between normal and abnormal gestational conditions.

—*R. T. Frank.*

## Miscellaneous

The third volume of *Post-Graduate Surgery,*[37] edited by Rodney Maingot, has appeared. This volume which totals 2,000 pages, has many contributors, all English. As differences exist between English and American surgery, these contributions are of particular value, especially in debatable fields in which technics and indications have not yet crystallized.

The section devoted to obstetric surgery, by Bourne, is divided into 6 chapters. He emphasizes *what* to do over how to do it. His indications are very careful and given in detail. For induction of labor he favors rupture of the membranes or bags, believing, as I consider justly, that endocrine methods have not yet proved their value. He then takes up version, forceps, among which the illustrations show some patients in the lateral posture, as well as destructive operations. He is against the low cesarean operation in infections and states that the Latzko technic is difficult.

—*R. T. Frank.*

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[30] **Endokrinologie für den Frauenarzt.** Von Professor Dr. Erwin Kehrer, Geh. Med. Rat, Direktor der Universitaets-Frauenklinik in Marburg. Mit 34 abbildungen, 564 Seiten. Ferdinand Enke, Stuttgart, 1937.

[31] **The Rabbit Test.** By S. B. Anklesaria, M.D., Honorary Obstetrician and Gynaecologist, Shet Vadilal Sarabhei General Hospital, etc., Ahmedabad. With a foreword by Dr. Emil Novak. 161 pages. H. K. Lewis & Co. Ltd., London, 1937.

[37] **Post-Graduate Surgery.** Edited by Rodney Maingot, F.R.S. (Eng.). Volume III. With 1015 Figures in the Text. 2,009 pages. D. Appleton-Century Co., Inc., New York, 1937.

This *Synopsis of Genitourinary Diseases*[38] which appeared first three years ago now comes out in a second edition. It is felt that the recent advances in the treatment of genitourinary diseases have been of sufficient importance to warrant a second publication. Among the changes that appear in this edition is a very complete discussion of the regulation of the diet which has lately assumed an important rôle in the treatment of infections, and is regarded as important in the control of calculus formation.

In the discussion of nontuberculous infections of the genitourinary tract, there have been outlined a number of diets including a high vitamin acid-ash diet, various modifications of the ketogenic diet, with a low caloric value, and sample menus and lists of food values.

In the section on cryptorchidism the use of gonadotropic hormones is discussed as to its value and method of administration. The largest dose mentioned is 300 rat units, three times a week. The discussion of urogenic and functional disturbances of the bladder has been elaborated. The re-written section on disturbances of the male genital functions, especially in regard to sterility, should be of interest to those investigating nonfertile married couples.

—*Philip F. Williams.*

This book, *Kidney Pain, Its Causation and Treatment*,[39] brings before the medical public the views of the author on the subject of obscure kidney pain. The ideas expressed represent the results of an experimental attack on the problem made during the past decade, and, in addition, an attempt to explain obscure pain from a clinical standpoint. Particularly in the investigations the author has tried to evaluate the relationship of the kidney-pelvis musculature to obscure kidney pain.

After a chapter on embryology and anatomy of the kidney, the author describes the technic of pyeloscopy and pyelometry, through which he is able to determine the tone of the kidney-pelvis musculature. He feels that more than one type of dysfunction of the kidney structure may co-exist in the same patient, and outlines an investigation which may rule out various factors, local and general. A similar handling of ureteral dysfunctions is given.

The study of the pharmacologic and pharmacodynamic action of drugs on the urologic system has been carried out experimentally on the anesthetized dog, and clinically by urologic investigation of patients. During this investigation the method of pyeloscopy and pyelometry has been utilized. It is stated that there are experimental and clinical inconsistencies in the action of adrenalin and estrine, if one postulates that the actions of autonomic and sympathetic are antagonistic. Recitals of clinical cases are appended. After discussing hydropelvis and hydronephrosis, the author outlines the indications and suggestions for treatment in such conditions.

It is felt that the value of pyeloscopy and pyelometry have not been sufficiently emphasized in previous studies of kidney pain and other complications. The technic is so easy that it should be added to both clinical and experimental research on this problem, the solution of which, it is felt, will be more rapidly advanced by a closer liaison between the physiologist and urologist.

—*Philip F. Williams.*

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[38]**Synopsis of Genitourinary Diseases.** By Austin I. Dodson, M.D., F.A.C.S., Richmond, Virginia. Professor of Genitourinary Surgery, Medical College of Virginia; etc. With 112 illustrations, 294 pages. Second Edition. The C. V. Mosby Company, St. Louis, 1937.

[39]**Kidney Pain, Its Causation and Treatment.** By J. Leon Jona, M.D., F.R.A.C.S., Hon. Asst. Gynaecological Surgeon, Women's Hospital in Melbourne. Illustrated, 94 pages. J. & A. Churchhill, Ltd., London, 1937.

The second edition of Warbasse's *Surgical Treatment*,[40] now Warbasse and Smyth, appears eighteen years after the first one. It is a one man job in 3 volumes of together 2,600 pages. As can be seen from the title, treatment is its sole purpose, both diagnosis and pathology being omitted. Presumably it is therefore meant for the practicing surgeon and as an adjunct for those medical men who participate in the choice of operation and aftertreatment. The entire field of surgery is covered.

Volume I deals mainly with the general principles of surgery, including anesthesia. Under anesthesia, local anesthesia for special operations is given in great detail. On the other hand, nutritive disturbances and endocrinopathies are summarily dealt with in 2 pages. There is a long and detailed chapter on the blood and blood vessels, with a well-illustrated portion dealing with the anatomy and the ligation of various major vascular trunks. Over 300 pages are devoted to the diseases of bones, fractures, dislocations, joints, and operations on these structures. Then muscles and tendons are discussed. A chapter dealing with the skin and appendages would appear to me more appropriate in a book on dermatology. A long roster of dermatologic lesions is given, with their treatment, which to the average surgeon or practitioner can be of little value unless he has received exceptional dermatologic training.

In Volume II the head, including the brain, the eye, ear, mouth, and nose, as well as larynx and trachea will be found. The spine, neck, thorax, breast, abdomen, stomach, spleen, and pancreas are likewise discussed in this volume.

The third volume covers hernia, rectum, vermiform appendix, liver and gallbladder; also the genitourinary organs, extremities, pelvis, amputation. Special chapters are devoted to plastic and cosmetic surgery. Surgery of the newborn, electricity and radium, first aid and bandaging, are discussed and concluding some chapters on economics. The index forms a special small volume of 131 pages.

This surgery covers an immense amount of territory in a very uneven fashion. Some subjects are dealt with in detail, as for example local anesthesia of the various regions, the ligation of larger vessels, tonsillectomy, appendectomy, etc. Other subjects are dealt with so cursorily as to prove of little value. The description of the major operations in most instances is far too sketchy to be utilized by any but the fully trained surgeon. I mention for instance, laryngectomy in one stage and transplantation of ureters into the sigmoid. Exceptions, in which a detailed description is given, are thyroid resection, amputation of the breast, the general principles of entering the abdomen and treating intraabdominal conditions. In these subjects the text is adequate and fully illustrated. In the operation for inguinal hernia, reliance is placed on the transversalis and the external oblique aponeurosis without transplantation of the cord. In femoral hernia the closure of the ring below Poupart's is stressed. The operation for cystocele does not conform to the most modern technic.

—*R. T. Frank.*

*Preoperative and Postoperative Treatment*[41] is a very detailed account of the most modern methods, particularly those practiced by the younger group in Boston. A number of others have aided the author in writing special chapters.

The book contains a tremendous amount of material, well arranged and readily accessible. The most modern methods of diagnosis and preoperative care are described in great detail for every type of surgical affection.

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[40]**Surgical Treatment.** By James Peter Warbasse, Special Lecturer in the Long Island Medical College, etc., and Calvin Mason Smyth, Jr., Assistant Professor of Surgery in the University of Pennsylvania Graduate School of Medicine, etc. Second edition, in three volumes, with 2486 illustrations, some in colors; 2617 pages. With added complete index. W. B. Saunders Co., Philadelphia, 1937.

[41]**Preoperative and Postoperative Treatment.** By Robert L. Mason, M.D., Assistant in Surgery of the Massachusetts General Hospital. Illustrated, 495 pages. W. B. Saunders Company, Philadelphia, 1937.

The chapter on anesthesia, the evaluation of surgical risks in different conditions, and every form of treatment utilizable in preparing a patient for and subsequent to operation, are very well handled. The author employs great care in giving the physiologic facts upon which different types of therapy are based. For example, his preliminary remarks introducing acidosis and alkalosis, show that he is aware that many medical men do not understand the underlying principles upon which the recognition and treatment of these disturbances are based.

Naturally in a book of this kind some improvements can be introduced. The chapter on shock is extremely short considering its importance. Whether every surgeon will agree that in heart and kidney diseases local anesthesia, supplemented by gas oxygen is to be preferred, is open to question. Likewise that in a diabetic, gas ether supplemented with ether or spinal anesthesia should be employed, is open to discussion. I note that only the most cursory mention of the sedimentation test, which certainly gynecologists find of tremendous help, is made. The bibliography appended at the end of each chapter should prove extremely useful. This is a good book.

—*R. T. Frank.*

During the World War, Dr. Guedel was concerned in the instruction and the supervision of the administration of anesthesia by untrained medical corps men. His observations in those days and his continuing interest in the subject in intervening years has resulted in a technic of teaching anesthesia which he presents in this new book, *Inhalation Anesthesia.*[42] The book is to be regarded as a fundamental guide, since the physiologic or pharmacologic mechanisms involved are discussed only in the line of clinical application.

The book is divided into two parts: Principles of Inhalation Anesthesia and Anesthesia Accidents. In the first part he discusses inhalation anesthesia by methods and agents, and continues with a discussion of the stages and signs, which he illustrates by means of graphic charts. The extent or depth of anesthesia required for the control of surgical reflexes is considered by systems and operation.

Surgery of the vagina is recommended to be performed under his suggested lower first plane. Normal delivery and low forceps extraction are also placed in this group. Deep anesthesia is not regarded as necessary to provide muscular relaxation in cesarean section. The major consideration here is the prevention of vomiting during the operation. The operation of internal podalic version and extraction is regarded as calling for anesthesia in the third plane. Bandl's contraction ring is considered to be amenable to the upper third plane. In the section discussing breech extraction the upper third plane anesthesia is considered until the breech is broken and one foot brought down, and the anesthesia then brought back to the upper second plane for extraction.

In discussing resuscitation of the infant, the author feels that this is facilitated if the maternal $CO_2$ level is high at the time of delivery. This may be utilized safely with head presentations, but the after-coming head calls for a low maternal $CO_2$ level for two or three minutes prior to delivery, or else premature inspiration, with resultant aspiration of fluid or débris, will occur. Hence with the $CO_2$ level low the first inspiration in breech extraction babies will be delayed as a rule. There is ample discussion of the preparation of the patient and selection of the anesthetic agent.

The second half of the book is devoted to a consideration of anesthetic accidents, difficulties and deaths under anesthesia. In this section the author discusses the various factors of blood pressure, ventricular fibrillation, central respiratory failure,

[42] **Inhalation Anesthesia.** By Arthur E. Guedel, M.D., Associate Clinical Professor of Surgery (Anesthesia), University of Southern California School of Medicine. 172 pages. The Macmillan Co., New York, 1937.

and peripheral respiratory interference. Other factors, as aspiration of débris, and various miscellaneous actions are considered, and there are chapters on cyanosis and anesthetic explosions. In discussing ventricular fibrillation he includes some case reports, and emphasizes the relation of psychic and emotional upheavals. There is a thorough consideration of the use of nitrous-oxide in obstetrics, and the author states that it is safe and desirable *in the hands of a well-trained anesthetist.* The frequent accidents and complications of vomiting during cesarean section is thoroughly discussed, as is also the author's consideration of pre-anesthetic sedatives. The book merits reading by all obstetric operators.

*—Philip F. Williams.*

The inaugural thesis representing five years of work by Ovidio Unti[43] includes both laboratory, animal, and human research with one of the barbiturates "dial." The author would limit its application to basic anesthesias supplemented by inhalation anesthesia. Forty-five human case histories are appended.

*—R. T. Frank.*

The *Surgical Studies*[44] written by Ribeiro and published in Brazil, cover a diversity of subjects. In all there are 17 articles. This, in a way, is a report of the surgical activity of the author, dealing with 842 patients on whom 559 major and 283 minor operations were performed, with 9 deaths.

There is an article on 10 cases of nerve lepromata in which surgical intervention was practiced mainly in the caseous stage. Postoperative intestinal paresis is taken up. There are several articles on pyloric hypertrophy in different age groups. Cholecystectomy is advised in conditions of cholecystitis in order to avoid future carcinoma of the gallbladder. The monograph is faultlessly gotten up with numerous illustrations.

*—R. T. Frank.*

Dr. Brookes has developed in this volume, *Textbook of Surgical Nursing,*[45] a very thorough and complete exposition of surgical conditions for nurses, and in addition has given a meticulously detailed manual of nursing technic.

In the sections of the book relating to nursing and operative technic he has followed the present set up used in the Barnes Hospital in St. Louis. After discussing the relation of the nurse to the surgical patient, some general surgical principles as inflammation, infection, wounds and tumors are taken up. In a number of following chapters the sequence of material runs through preparation and sterilization, routines of pre- and postoperative care, while the modern anesthetic agents are discussed as to their possible disadvantages or dangers. The author regards cyclopropane and evipol as still in the experimental stage. The three chapters on the operating division might well serve as ground work for organization and also for comparison by established services.

The subject matter of most of the remaining text is devoted to a comprehensive discussion of surgical condition and surgery, of the various systems. Dr. T. S. Brookes has contributed the chapter on orthopedic surgery, Dr. E. A. Graham and Dr. E. Sachs have contributed to the sections on chest surgery and neurologic surgery. Dr. H. S. Crossen has written the chapter on gynecology. The ingenious vaginal operation drape described has merited two full page illustrations, Figs. 36

[43] **Anestesia de base pela Dialilmalonilurea.** Thèse Inaugural, apresentada a Faculdade de Medicina do Paraná, 1936.

[44] **Estudos Cirurgicos.** Enrico Branco Ribeiro, Cirurgião da Beneficiancia Portugesa e do Sanatorio Santa Catharina. São Paulo, Brasil, 1936.

[45] **Textbook of Surgical Nursing.** By Henry S. Brookes, Jr., M.D., Instructor in Clinical Surgery, Washington University School of Medicine, etc. With 233 illustrations, 636 pages. The C. V. Mosby Company, St. Louis, 1937.

and 172. In the closing chapters of the book are found discussions on complications, special procedures and surgical diets. The book closes with a list of medicolegal points. This is an excellent book for the surgical nurse or surgical resident.

—*Philip F. Williams.*

In this manual, *Operating Room Procedures*,[46] bound in an utilitarian loose-leaf fashion, Miss Hoppe and Miss Halverson have produced a guide for all who are concerned with the handling of operating room routines. This book should be of utmost advantage not only to the operating room supervisor, but to the surgical internes and staff as well. Included in the table of contents are sections on a general outline of the routines for the personnel, care and preparation of materials, draping, and various special trays and instrument set-ups. In the remainder of the book surgery is divided by systems, under each system pertinent operative procedures are given. Each procedure is discussed from the operating nurse's standpoint with a brief statement of the purpose of the operation, position and draping for the operation, technic, sutures and instruments used.

The book offers an excellent example of the manner in which the organization of a particular division of a hospital may be accomplished. The type of binding used will render changes and revision an easy matter.

—*Philip F. Williams.*

*Some Fundamental Aspects of the Cancer Problem*[47] is published by the American Association for the Advancement of Science and edited by Henry Baldwin Ward. It deals with the many-sided survey of the great field of the unsolved problem—the cancer question. The many papers contained in this monograph were presented at the Atlantic City Meeting. They cover heredity and constitutional factors; induction, stimulation and inhibition of tumorous growths; metabolism of cancerous tissues; radiation; and a general discussion of the cancer problem.

Under heredity and constitutional factors, the seven articles all deal with the mouse. In the second subdivision, mainly the chemical aspects resulting from the fact that the sex hormone and carcinogenic agents resemble each other chemically and physiologically, are dwelt upon. The metabolism of cancer tissue deals largely with the effect that cancer has upon the body metabolism.

These short articles with their appended bibliographies are an excellent medium to review the present status of this all important question.

—*R. T. Frank.*

This volume, *Emotional Adjustment in Marriage*,[48] has been written to help the physician who may meet in his practice the problems of sexual difficulties in marriage. The various chapters discuss the nature of the sex desire, the deviations, rather than the abnormalities, from what is regarded as normal in this respect, and the assumption of those attitudes and practices in marriage and the sexual relation which are calculated to assist one to the attainment of the greatest possible happiness in such a relation.

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[46] **A Manual of Operating Room Procedures.** By Almira W. Hoppe, Science Instructor, Jewish Hospital of St. Louis, and Lucile M. Halverson, supervisor of Operating Rooms, University of Minnesota Hospitals. University of Minnesota Press, Minneapolis, 1937.

[47] **Some Fundamental Aspects of the Cancer Problem.** Symposium Sponsored by the Section on Medical Sciences of the American Association for the Advancement of Science, Atlantic City, New Jersey, December 29, 1936—January 1, 1937. Edited by Henry Baldwin Ward. 248 pages. The Science Press, New York, 1937.

[48] **Emotional Adjustment in Marriage.** By LeMon Clark, M.D., Assistant in Obstetrics and Gynecology, University of Illinois College of Medicine. 261 pages. The C. V. Mosby Company, St. Louis, 1937.

The subject of birth control is dwelt upon philosophically, as to its principles and cosmic effect, as well as in a practical manner with a discussion of present available methods and devices. The premarital consultation (Dickinson) is regarded and discussed as an element of preventive medicine.

It is very unlikely that all of the author's views and conclusions will be universally accepted, although a reading of it should be helpful in assisting some physicians to deal with psychic problems in married patients.

—*Philip F. Williams.*

*Sexual Power*[49] by Chester Tilton Stone is designed for informing the lay public and the general practitioner. According to the author, less than 50 per cent of civilized men enjoy full sexual potency. In the mind of the average woman, sex is too often associated with hypocrisy and humiliation.

This is a well written and clearly put book covering the subject of potency, impotency (psychic, functional and organic), the psychic and physical basis of sex difficulties as well as the effect of the endocrine glands upon sexual power. I am surprised to see the prostate put among the endocrine glands even if with some reservations. There are such occasional misstatements as—if the anterior lobe of the hypophysis is predominant, masculinization results, if the posterior lobe, femininization, for which statements there is not the slightest proof.

On the whole, this subject is approached from the proper attitude and from the proper point of view. It covers the subject adequately. In my opinion, a number of the brief case histories might well have been omitted without impairing the text.

—*R. T. Frank.*

This manual on contraception entitled *Marriage and Periodic Abstinence*[50] is written by J. G. H. Holt who includes among his titles that of "sexologist." Evidently, to this extent, specialization in such matters exists in Holland. He divides the subject matter of intentional birth control into three parts. In the first he deals with the historical aspects of conception and ovulation and then proceeds into the biologic researches coincident with Ogino's discovery. He discusses such objections to Ogino's theory as the proposition that several ovulations may occur in one cycle, that the duration of the cycle may vary under the influence of abnormal circumstances, that the theory is invalid in cycles of from twenty to twenty-two days, and finally, that so-called "violent-ovulation" might be provoked by the sexual act. In discussing the abnormal pathologic conception period, he mentions that we should bear in mind that ovulation is a biologic process and that we cannot control the subtleties of nature. Various symptoms commonly mentioned as suggesting the occurrence of ovulation are described. Detailed rules and directions for practice of the Ogino method are given, but in an intricate and confusing style.

In the second part of the book he discusses the reversal of this method as a therapeutic measure in infertile couples. A general number of test cases with their accompanying menstrual calendars are appended as a third part, and a datometer or calendar measuring device is included with the book. A very full discussion of the intricacies of the method should make the book of interest to those who are engaged in explaining such methods to their patients.

—*Philip F. Williams.*

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[49]**Sexual Power.** By Chester Tilton Stone, M.D., Clinical Assistant Surgeon, Urological Department, Bellevue Hospital, New York, etc. Illustrated, 160 pages. D. Appleton-Century Company, New York, 1937.

[50]**Marriage and Periodic Abstinence.** By J. G. H. Holt, M.D., Gynecologist and Sexologist, The Hague and Harlem, etc. 174 pages. Longmans, Green and Co., New York, 1937.

The importance of laboratory tests for syphilis is undoubtedly increasing, and under the impetus of the recently awakened public interest in syphilis, the reliability of such tests will no doubt frequently be questioned. Of interest to physicians then will be this book, *Laboratory Diagnosis of Syphilis,*[51] which by its presentation of the clinical evaluation of the serologic report will be found especially valuable.

The text describes the history of the development of various serologic tests, devotes seven chapters to the Wassermann reaction, four chapters to the flocculation tests and gives a lengthy discussion of the examination of the spinal fluid. Various other tests for syphilis are more briefly taken up.

The section on the clinical evaluation of the serologic reports discusses, especially, the various types of falsely positive reactions. Since in many conditions, as in pregnancy, where syphilis is characterized by a long period of latency, a positive serum is the only objective evidence of the presence of the disease, it behooves the physician to have a definite understanding of the various reports which may be rendered. In discussing cord blood Wassermann reactions, the author states that serologic findings in the cord blood usually reflect the maternal blood findings, and are worthless as a diagnostic test for the presence of syphilitic infection in the newborn. The behavior of the infant's Wassermann taken week after week is, however, regarded as a valuable and frequently the only, clue to such infection. Further it is noted that the reports of the past decade make it reasonably certain that neither pregnancy, anesthesia, nor malignancy predisposes to false positive reactions.

—*Philip F. Williams.*

Coincident with the recent widespread attempt of the public health organizations of the United States to eradicate syphilis, the appearance of this small book, *Syphilis: The Next Great Plague to Go,*[52] is timely. Dr. Fishbein, the editor of the *Journal of the American Medical Association,* has prepared this discussion of the disease in his usual inimitable style. The story as he tells it, is complete and explanatory as to the nature, transmission, social and economic aspects of the disease, and of the various methods by which it may be treated and eradicated.

The chapter on the "Prevention of Syphilis in the Prospective Mother and Child" should be read by every obstetrician and married couple, for as Parran has said, "proper oversight of the pregnant woman could eradicate congenital syphilis completely." In the chapter on "When Syphilitics May Marry" the author has included memorandum relating to the legal aspects of the marriage of syphilitics in the various states, and the medical advice given on page fifty-seven insures both parties to the marriage, when one is syphilitic, a square deal.

This book deserves to be read by every adult in the United States.

—*Philip F. Williams.*

A continued demand for an authoritative textbook on this constantly developing mode of therapy has led Krusen to revise his *Light Therapy.*[53] In the general revision of the book fifty-two pages have been added, while the chapter on physiology has been much enlarged. Many new photographs and illustrations have been added.

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[51]**Laboratory Diagnosis of Syphilis.** By Harry Eagle, M.D., Passed Assistant Surgeon, United States Public Health Service, Washington, D. C., etc. With foreword by J. Earle Moore, M.D., Associate in Medicine, Johns Hopkins University, etc. The C. V. Mosby Company, St. Louis, 1937.

[52]**Syphilis: The Next Great Plague to Go.** By Morris Fishbein, M.D., Editor, Journal of the American Medical Association and of Hygeia, the Health Magazine. David McKay Company, Philadelphia, 1937.

[53]**Light Therapy.** By Frank Hammond Krusen, Associate Professor of Physical Medicine, The Mayo Foundation, University of Minnesota, etc. Second edition, revised, and enlarged. With 42 illustrations, 238 pages. Paul B. Hoeber, Inc., New York, 1937.

Undoubtedly light therapy will be found beneficial in many general conditions which come under the notice of obstetricians and gynecologists. At present there seems to be no definite indication for its use in most of the specific diseases met in these two specialties.

—*Philip F. Williams.*

*Medical Morals and Manners*[54] by Royster contains papers and addresses written or delivered by the author during the last forty years. In one of these papers he says, "No man should be permitted to indulge in reminiscence until he has passed at least beyond the age of fifty years. Before that time usually his outlook is too recent, his experience limited, and his philosophy unseasoned. On the other hand, if he waits until senility overtakes him, his observations may be tinged with maudlin sentiment and hazy forgetfulness."

Many subjects are covered in a simple, attractive way, equally understandable to the medical profession as well as the laity. Medical ethics can be boiled down to the standards of honor and fair dealing with associates and customers. Eighty per cent of the general practitioner's patients are women and therefore he should understand them. He classifies the types of modern doctors into political, business, social, near-quack, the symptom doctor, and the ideal doctor.

Such subjects as athletics and scholarship, physical standards for women, and physical morality are dealt with. He emphasizes that "surgical sense" is of utmost importance and says, "Let us ask to be delivered from the cocksure surgeon. There are many good operators but few good surgeons." A chapter on facts about appendicitis for the laity is included. The book makes pleasant reading.

—*R. T. Frank.*

These are *Papers from the IV Medical Service of St. Erik's Hospital, Stockholm.*[55] In this collection of monographs, not only papers from St. Erik's Hospital in Stockholm, but from Hammarsten's Biochemical Laboratory are reported in collaboration. The majority of the articles are in Swedish. Several, however, appear in English.

The papers mainly cover tests applying to kidney function and hematology, as well as some dealing with pancreatic and gastric investigations. One investigation, with a fairly pure secretin, was performed on the human being and this was also used as a test for pancreatic function. Of the articles in Swedish, there is a profusely illustrated one dealing with the glands of internal secretion.

—*R. T. Frank.*

Volume I of the *Annals of the Faculty of the Medical Sciences of the National University of the Platte*[56] at Buenos Aires contains many articles by different members of the faculty, both medical and surgical.

There are several communications on diphtheria and its treatment. Likewise one on the serum treatment of erysipelas, an interesting article on tenia saginata, as well as on the distribution of intestinal parasites in Argentine; also one on 2,700 cases of amebiasis, showing how widespread the infestations are in this region.

Of the surgical contributions, the one on ureteral lithiasis, recurrent hydatid in the pouch of Douglas, the etiology of celiac diseases are of interest. Of the technical surgical subjects dealt with is Reichel-Polya gastrectomy for ulcer, two on fractures of the femur, one by the open method, the other by the closed method, and three

[54]**Medical Morals and Manners.** By Hubert Ashley Royster, M.D. 333 pages. Chapel Hill, The University of North Carolina Press, 1937.

[55]**Papers from the IV Medical Service of St. Erik's Hospital, Stockholm.** Edited by Hilding Berglund. 269 pages. Alb. Bonniers Boktryckeri, Stockholm, 1937.

[56]**Anales de la Facultad de Ciencias Medicas de la Plata.** Tomo I. Buenos Aires, 1937.

contributions on the treatment of osteomyelitis. These articles show the type of work that is being performed at the university.

—*R. T. Frank.*

*Twenty-Five Years of Health Progress*[57] is a statistical report of 611 pages by Louis I. Dublin and Alfred J. Lotka of the Metropolitan Life Insurance Co. It covers the period of 1911 to 1935 and deals to a great extent with the mortality of those insured in the company. There has been a steady gain in life expectation during this period. This report will interest particularly health officers, physicians, sociologists and life insurance officers.

In the last twenty-five years, the average duration of life has been extended by fourteen years through public hygiene agencies and the advance in medicine. For example, the tuberculosis death rate among the insured has dropped from 242 to 56 per 100,000. There has also been an advance in the standard of living. These statistics represent a huge cross-section of the entire population as there were 17,000,000 weekly paying policyholders in 1935. The main number are composed of urban wage earners.

These statistics should interest the obstetrician and gynecologist greatly as 56 per cent are females while in the general population, females represent only 49.5 per cent. Of the insured, 3,200,000 died, which represent 9.2 of every 1,000 of insured each year.

Of the communicable diseases, tuberculosis, influenza and pneumonia play the greatest rôle. Cancer of the female genitals occurred in 52,700, exceeded only by cancer of the stomach and liver, forming a group of 84,000. In these twenty-five years, there is no evidence of increase of carcinoma of the female genitals.

The puerperal state was responsible for 55,141 deaths. In the general population, the authors add, 375,000 deaths occurred from this same cause. The mortality of puerperal sepsis was 38.5 per cent, puerperal toxemias, albuminuria, 23.1 per cent, all the other puerperal causes which represent sepsis, hemorrhage, etc., 38.5 per cent. There was a decline of 20 per cent in deaths from these causes.

—*R. T. Frank.*

Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix by the *Health Organization of the League of Nations*[58] is a short statistical pamphlet, the first of a series of annual reports. The committee consists of Dr. J. Heyman of Stockholm, the editor, Dr. Lacassagne of Paris, and Lt.-Col. A. B. Smallman of London.

Future reports are to include analyses of material relating to cancer of the corpus uteri as well as that of the vagina. A report from the University of Brussels of cases treated in 1930 shows the absolute cure rate 14.9 per cent. In the Liverpool Radium Institute there is no absolute cure rate given. From the Marie Curie Hospital in London, the absolute cure rate is 39.4 per cent. From the London Radium Center, it is 15.2 per cent. From the Radium Institute of Paris University no absolute cure rate is offered. From the Radiumhemmet, Stockholm, it is 24.4 per cent.

These tables should prove of increasing value as statistical uniformity is arrived at.

—*R. T. Frank.*

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[57]**Twenty-five Years of Health Progress.** A Study of the mortality experience among the Industrial Policyholders of the Metropolitan Life Insurance Company 1911 to 1935. By Louis I. Dublin, Ph.D., and Alfred J. Lotka, D.Sc., with the collaboration of the staff of the Statistical Bureau. 611 pages. Metropolitan Life Insurance Co., New York, 1937.

[58]**League of Nations Health Organization.** Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix. First Volume. Statements of Results Obtained in 1930 and Previous Years (collated in 1936). Edited by: J. Heyman, M.D., Stockholm. 74 pages. Columbia University Press, New York City.

This book, *Mortality Trends in the State of Minnesota,*[59] by Calvin F. Schmid, brings together in compact form significant statistical data regarding mortality in that state and should be of interest to those of the medical and allied professions who are concerned in public health problems. The study covers the mortality experience of Minnesota from 1910 to 1935, and demonstrates that during this period of twenty-six years the general mortality rate has fallen from 11.2 to 8.2. The minimum rates approximate the period of economic depression which began in 1929. The author speculates on the causative factors.

The trends in the principal causes of death for the period are discussed, and the more important causes are considered in detailed form for the biennial period of 1932 and 1933. Here it has noted that cancer of the uterus accounted for 7.2 per cent of the cancer deaths, in other words this condition holds fifth place with 934 deaths.

During this biennium premature birth with 1476 deaths, held seventh place. Injuries at births, with 499 deaths, held seventeenth place. Diseases of pregnancy, childbirth, and the puerperal conditions, with 416 deaths, ranked in twentieth place. Because of the stigma attached to the certification of deaths from syphilis, it is recognized that the death rate from this cause cannot be considered reliable.

Mortality is also discussed from the standpoint of age and sex, as are also the mortality trends. The expectation of life at birth for females in Minnesota is given as 65.2 years. The excess of mortality among wives for the younger ages is ascribed mainly to the hazards of childbearing. Eighty-five per cent of the deaths attributed to gonococcal infection were in females. One-third of all cancer deaths, uterus and other female genital organs, were in women of sixty-five years of age, and there were only three such deaths recorded under thirty years of age.

Infant mortality rate in Minnesota has undergone a significant and continuous decline. Among the factors contributing to this downward movement has been the definite program for infant welfare, which includes the education and prenatal care of expectant mothers. The birth rate in Minnesota is dropping. The number of stillbirths in Minnesota has remained practically stationary. There has been a slight decline in the maternal mortality rate in Minnesota during the twenty-six-year period with two high peaks shown in the post-influenza years. A minimum maternal mortality rate of 4.3 per 1000 live births was recorded in 1929. Puerperal septicemia was followed in order by toxemia of pregnancy, hemorrhages of pregnancy, and other accidents, as the most frequent causes of the puerperal state.

Other chapters deal with the seasonal variations of mortality, and with comparative statistics regarding maternal mortality, and other causes of death in the registration area of the United States.

—*Philip F. Williams.*

*Intimate Side of a Woman's Life*[60] is the suggestive and for this reason somewhat objectionable title of a most useful small volume by Leona W. Chalmers. After a brief and correct description of the pelvic organs the author speaks of constipation, leucorrhea, contraception and general body hygiene. The specific value of this book lies in the intelligent form in which such common procedures as enemas, vaginal douches, certain exercises, etc., are described. In referring his patients to this book the physician will save much time and know that these procedures will be carried out in a proper manner.

—*Hugo Ehrenfest.*

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[59] **Mortality Trends in the State of Minnesota.** By Calvin F. Schmid, Assistant Professor of Sociology, University of Minnesota. 317 pages. The University of Minnesota Press, Minneapolis, 1937.

[60] **Intimate Side of a Woman's Life.** By Leona W. Chalmers. Illustrated, 128 pages. Pioneer Publications, Inc. Radio City, N. Y., 1937.

# Department of Reviews and Abstracts

Conducted by Hugo Ehrenfest, M.D.

## Collective Review

### RECENT LABORATORY TESTS FOR THE EARLY DIAGNOSIS OF PREGNANCY

A Critical Review of Recent Experimental Work

Abner I. Weisman, M.D., New York, N. Y.

*(From the Department of Gynecology and Obstetrics of the Metropolitan Hospital)*

NO TOPIC in obstetrics is receiving more world-wide study at present than diagnostic laboratory tests for early pregnancy. The medical journals are filled with many new and varied tests, and the claims of some authors are at times nothing short of miraculous. These enthusiastic reports have led the average physician to try some of the tests with, in many cases, embarrassing results. So involved have most of us become in trying to sift out the worthy tests from the less valuable and worthless tests that the entire problem has become quite confusing. Prior to 1928 and the advent of the Aschheim-Zondek test, there were some few suggested laboratory methods for diagnosing early pregnancy; i.e., Abderhalden's serodiagnostic test[1] of the protective ferments in pregnancy, and the tests based on glycosuria in pregnancy, which included the phloridzin test of Kammitzer[2], the glucose tolerance test of Frank and Nothman[3] and the adrenalin-glycosuria test of Roubitschek.[4] These tests were never considered feasible and with the coming of the Aschheim-Zondek test and its remarkable accuracy, these early tests have mostly been forgotten and are herein mentioned only for the sake of academic interest. This paper is an attempt to survey the mass of literature dealing with pregnancy tests in more recent years and to compare the results obtained by different investigators.

#### ACCEPTED ROUTINE TESTS FOR PREGNANCY

*The Aschheim-Zondek Test.*[5]—This widely known test is now nine years old and employs the use of immature female mice weighing less than 8 gm. and about three weeks of age. Five mice are injected subcutaneously with filtered morning urine of the suspected case three times daily in doses of ½ c.c. each injection; ninety-six hours after the first injection the animals are killed, their abdomens opened, and the ovaries inspected. A positive reaction consists of enlarged hyperemic ovaries with small pinpoint blood spots dotting the surface. These are corpora hemorrhagica. The presence of corpora lutea makes the diagnosis even more conclusive. This specific ovarian stimulation is due to the presence of large amounts of anterior pituitary-like hormone which is found in the urine of early pregnancy. In 2,000 cases tested by this method by Aschheim,[6] he obtained 98 per cent correct positive reactions and 99.5 per cent correct negative reactions. Other investigators (eleven independent groups reported by Mazer and Goldstein[7]) using the same tech-

nique or some slight variation, performed the tests on 2,807 cases and obtained on the average, correct positives in 94 per cent and correct negatives in 97 per cent of the cases. More recently Mack and Agnew[8] reported the work of 19 other investigators who tested 8,685 cases with the Aschheim-Zondek test and found an average accuracy of 96.6 per cent. In 1935 Aschheim mentioned[6] that up to 1933, investigators who worked with this test reported 11,345 urine examinations with only 1.8 per cent false results.

It thus is evident that the Aschheim-Zondek test is a most valuable addition to the armamentarium of the physician and laboratory worker. Recently Davy and Sevringhaus[9] using slight variations of the Aschheim-Zondek technique in undiagnosed and borderline cases, managed to obtain 90 per cent correct results when one test was used alone and much better results when a correlation of two methods was put in use. Other investigators employed rats in the test and Reiprich[10] found that rats are more sensitive and more rapid in reaction than mice, since injections of 10 to 25 c.c. of urine into immature rats could be tolerated, and the reaction could be determined in from twenty-four to thirty-six hours. According to Reiprich a positive reaction in immature rats consists in hyperemia and hypertrophy of the ovaries to 3 or 4 times the size of the immature ovaries. More recently Mull and Underwood[11] tested 702 urine specimens by injecting immature rats with 2 c.c. of urine daily for five days and killed the animals on the sixth day. Working under suboptimal conditions their results were 91 per cent accurate, which upon consideration of the obstacles imposed were remarkedly good. The possibility of the rat taking the place of the mouse as a pregnancy indicator is not a likely one, but in many cases where the urine has proved too toxic for the small mouse, the larger animal might be used to good advantage.

Sar-Louis[12] performs the Aschheim-Zondek test with mature mice and points out a difference in response of the mature animals to urine of pregnant or nonpregnant women. The difference, however, is not very striking and his suggested variation does not look very promising.

*The Friedman Test.*[13]—This test, originated soon after the Aschheim-Zondek test, represents a simple modification, employing female rabbits, kept isolated, instead of mice. According to the original technique of Friedman (of which today there are many modifications) the rabbit is given 6 intravenous injections of urine in 4 c.c. doses during forty-eight hours, after which the animal is killed and the ovaries examined. Variations of the technique include a single injection of 15 c.c. of urine or a 10 c.c. injection on each of two days. Formerly the animal was killed and thus used for only one test, but it actually can be used a few times by opening the animal dorsally and replacing the ovaries each time after inspection. The results obtained by Friedman and Lapham,[13] in their original paper, were 100 per cent correct positives and negatives. A comparison of later reports by Mazer and Goldstein[7] shows that up to 1932 six independent workers obtained 99 per cent correct negative and 96 per cent correct positive results in 535 cases with the rabbit test. Up to 1933 Mack and Agnew report a 98.5 per cent accuracy obtained by 15 different and independent authors who tested 1,899 cases. Ware and Main[14] reported 99 per cent accuracy in 100 cases, and Young, in 1934, recorded the same degree of accuracy in 350 cases.[15] Spielman[16] performed 635 Friedman tests and maintained that the test "warrants universal adoption." Sharp[17] in New Zealand found the test 98 per cent correct, and recently Gernez,[18] Borras,[19] and Lejwa and Fryszberg,[20] found the test almost 100 per cent correct.

Best and McHenry[21] used two rabbits for each test and out of 538 tested urines obtained 251 positive reactions with 1.6 per cent error and 287 correct negatives with 2.1 per cent error. King[22] reviewed the literature and with 4,500 rabbit tests found

the gross error to be 3.9 per cent and a corrected error of 1.8 per cent. Goldberger, Salmon and Frank[23] performed duplicate tests on 1,093 pregnant women and found only 0.55 per cent false negatives and 0.09 per cent false positives. Feresten, in 1937, using a modified Friedman technique[24] tested 1,600 unknown urines with a total error of 0.94 per cent.

Kelly and Woods[25] recently gave many details and finer points in the technique of the rabbit test which when adhered to undoubtedly make the percentage of error even smaller. Evans, Kohls and Wonder[26] presented a new graphic curve of anterior pituitary-like hormone output in pregnancy, showing a maximum in the first trimester of pregnancy. Their work gives a satisfactory explanation for the accurate results obtained so early in pregnancy by the Aschheim-Zondek and Friedman tests. Schwarez[27] suggested the use of blood plasma instead of urine in the Friedman test and reported excellent results in a small series of cases. His work requires further study.

*Comparison of the Aschheim-Zondek and Friedman Tests:* Many laboratory workers adhere to one or the other of the two tests, and it is simply a question as to which test one is accustomed. Aschheim and his followers maintain that the mice are infallible while Friedman and his supporters claim that the rabbit is more advantageous because the test is quicker, more economical and the rabbit is less easily killed by toxic substances and less bothersome as a test animal.

In summarizing the comparative value of the two tests Crew[28] states that both the Aschheim-Zondek and the Friedman tests are 99 per cent perfect. Crew maintains that "a 90 to 95 per cent accuracy is not sufficient. . . . No test which yields more than 1 per cent of error can claim much support." Dawson[29] finds the mouse and the rabbit tests 99 per cent correct and positive within fourteen days after conception. Mack and Agnew compared the two tests in 1,110 cases and found them equally exact. As more refined techniques are being introduced the personal error in each case will eventually dwindle and both tests at some future date should prove 100 per cent accurate in trained hands.

## GONADOTROPIC HORMONE TESTS USING MALE RODENTS

*The Brouha Test.*[30]—Brouha and his associates used immature male mice and injected them in a manner similar to the Aschheim-Zondek technique. The test is based on an increase in size of the seminal vesicles in the male mouse after being subjected to pregnancy urine stimulation. Brouha reported a small series of cases, in which however, he had obtained excellent results. White and Severance[31] encountered 10 false positives in a series of 27 nonpregnant women. If this test can be proved to be accurate in a large series of cases it would be of great value.

*The Zaharesco Test.*[32]—Zaharesco-Karaman and his associates more recently reported a test for pregnancy which is a variation of the Brouha test. Rats are injected daily with 1 c.c. of blood or urine of pregnancy and after seven to ten days the animals are killed and a ratio is taken between the weight of the seminal vesicles in mg. and the weight of the rat in grams. If the ratio is more than 1 the reaction is considered positive. This test can in no way hope to supplant any of the accepted tests since seven to ten days are required before the reaction can be read. The computations are much more involved and complicated than even in Brouha's test.

## THE ESTRIN TESTS FOR PREGNANCY

*The Mazer-Hoffman Test.*[33]—This diagnostic test is based on the presence in the urine of pregnancy of large amounts of estrogenic substances which produce when injected into immature or castrated mice or rats an epithelial desquamation in the

vagina characteristic of estrus. The test runs for ninety-six hours and vaginal smears are taken daily. The results obtained by Mazer,[33] and Bland[34] show that the test is a poor diagnostic test for pregnancy, since it yields only 75 per cent correct positives. However, the correct negatives in nonpregnant women are 97 per cent accurate. This test is then worth far more as a test for ruling out pregnancy than for actually establishing the diagnosis of pregnancy.

*The Kelly Test.*[35]—Kelly introduced a simple variation of the estrin test by merely observing the extent of patency of the vaginal orifice of albino rats. After an intraperitoneal injection of 5 to 15 c.c. of pregnancy urine, a premature opening of the vaginal canal in from seventy-two to eighty-four hours is considered diagnostic for pregnancy. Hulpieu, Weatherby and Culbertson found[36] that the Kelly test is not better than the Friedman test; that it takes double the time, has a high mortality rate, and in the 59 cases tested gave more false positives than the Friedman test. However, Kelly's observation should be kept in mind when performing the routine Aschheim-Zondek test as it may serve as a corroborative test before the ovaries are inspected.

## FISH TESTS FOR PREGNANCY

*The Female Bitterling Test.*—There have been many tests for early pregnancy suggested by using fish as the laboratory animals but none of these have shown much worth. Fleischmann and Kann, in 1932,[37] first described the lengthening of the ovipositor of the female bitterling as a diagnostic test for pregnancy. The fish which normally is found in the rivers of central Europe possesses an external egg-laying tube, the ovipositor. During normal breeding season, the female extrudes the ovipositor and allows the ova to drop out and be fertilized. Fleischmann and Kann procured this elongation at will by merely adding urine of pregnancy to the water in the tank. Szusz,[38] in 1933, showed that this test was not specific for pregnancy. Kanter, Bauer, and Klawans,[39] more than a year after Szusz had completed his work, compared this fish test with the Aschheim-Zondek test and obtained exceedingly promising results. They suggested its use anew as an indicator of pregnancy. Owen[40] repeated the tests with the female bitterling and also thought it to be a good test for pregnancy notwithstanding the fact that his results were only 75 per cent accurate. Kleiner, Weisman and Barowsky repeated the work of Szusz but demonstrated that the so-called pregnancy reaction could be brought about as well by male urine, urine from postmenopausal women and nonpregnant single girls.[41] This observation was supported by Glaser and Haempel[42] Kotz, Douglas, and Parker,[43] Gottlieb,[44] and Moses.[45] The female bitterling test has since been shown by Kleiner, Weisman, and Mishkind[46] to be due to the presence of the male sex hormones and substances of closely related structural formulas.

*The Male Bitterling Test (Coloration Test).*—The male bitterling has been used by Tozawa[47] as a diagnostic animal for pregnancy determination, on the basis of a change in its color when urine of pregnancy is added to the fish in the aquarium. The attainment of the reddish coloration is neither exact nor has it been found of scientific value, since the personal error in differentiating between positive and negative readings is too great.

*The Stichling Melanophore Reaction.*—Mandelstamm[48] showed that a species of fish known as the Stichling underwent a darkening in color after being exposed to pregnancy urine for only two hours. Scant data were given by the author and only a 75 per cent accuracy was reported. The use of fish as experimental laboratory animals in the field of sex hormones is only recent, yet the rapid physiologic change which takes place in these cold blooded animals may in the very near future, open a vast field in the "scarcely touched-upon world" of the sex hormones.

## FROG TESTS FOR PREGNANCY

*The South African Frog, Xenopus Laevis.*—Shapiro and Zwarenstein,[49] in 1935, used a frog as a pregnancy indicator and found that out of 132 tests, 64 checked correctly in pregnant, and 68 checked correctly in nonpregnant individuals. The test consists of an injection of a prepared urine of pregnancy, followed by stimulation of the reproductive cycle in from six to twelve hours. In the South African female, claw-toed frog, after the injection the eggs are found in the cloaca, or if the reaction is not so strong they are found in the oviducts. This test is excellent and the error is practically negligible. The only drawbacks, which are very important ones, are that the frogs are obtainable only in South Africa and become useless after one month, thus necessitating a continuous fresh supply.

*Frog Melanophore Reaction.*—Konsulov[50] used hypophysectomized frogs *(Rana esculenta)* and injected 2½ c.c. of urine into the lymph sac of the frog. Pregnancy urine causes the skin of the frog to darken in 1 to 2 hours. Bruhl and Rieckhoff,[51] in 1935, repeated the Konsulov reaction in which pigment reappears in hypophysectomized frogs after the urine injection, and found that the test was not accurate unless the urine was concentrated eight times in volume. However, they found that other conditions besides pregnancy caused the darkening of color. Four cases of carcinoma and one out of three cases of tuberculosis and one case of gonorrhea gave the reaction. The melanophore test cannot be recommended until further work is done. Stabilization of certain factors might lead to a valuable test for pregnancy.

## ALLERGIC SKIN TESTS FOR PREGNANCY

The Gruskin intradermal test for pregnancy.

The intradermal anterior pituitary-like hormone test of Gilfillen and Gregg.

*Gruskin Intradermal Test for Pregnancy.*—In 1936 Gruskin[52] reported excellent results with a simple intradermal pregnancy test. All that is necessary is to inject intracutaneously a few minims of an especially prepared placental extract. In ten minutes the diagnosis of pregnancy could be established or disproved by the presence or absence of a local erythematous reaction with pseudopodia. Gruskin explained the manifestation on an allergic basis, and suggested the possibility of production of a new protein-like substance by the placenta which is foreign to the nonpregnant woman. More recently Schwartz[53] repeated Gruskin's work and obtained 96 per cent correct positives in 155 cases and 90 per cent correct negative reactions in 66 cases. These results appear at first glance to be fairly good, with so simple a test. However, the test is not applicable to various types of cases. Women with disturbances in metabolism, with endocrine and skin abnormalities, and allergic individuals who are sensitive to many types of proteins will undoubtedly show false reactions with such a skin test. Schwartz, himself, mentioned other limitations of the test. "A thorough knowledge of the fundamentals of wheal formation is essential to any one who expects to employ skin testing extensively." The personal error in interpreting the different types of reactions and the individual reactions of susceptible patients make this test useful only in the hands of a specialist in allergy. Perhaps with further study and standardization this test can be made useful to the average practitioner. If Dr. Schwartz himself reports six cases as erroneously positive out of 60 nonpregnant women, there still remains much more investigation to be done before the average physician could adopt this test.

*The Intradermal Anterior Pituitary-like Hormone Test.*—Gilfillen and Gregg[54] recently reported another intradermal test claiming that it is even more sensitive than the Aschheim-Zondek test in certain borderline cases. An injection of a few minims of antuitrin-S intradermally produces a wheal and redness in nonpregnant females under thirty years of age. In the pregnancy cases, no skin reaction is noticeable

after injection. This same test previously had been performed by Porges and Pollaczek,[55] and by Deutsch,[56] and Strauss.[57] All three investigators were convinced that the anterior pituitary hormone test was not accurate enough for pregnancy diagnosis. Recently the *Journal of the American Medical Association,* on two different occasions,[58, 59] did not lend its support to this intradermal test, due to its inaccuracy. Weisman and Yerbury[60] were the first to show that even with the identical commercial product and the same technique, used by Gilfillen and Gregg, the test was valueless. Later, Schneider and Cohen[61] repeated the test on a larger series of cases and corroborated the findings of Weisman and Yerbury. They concluded: "The results obtained with antuitrin-S injected intradermally in no way exhibit the reliability of this test as a means of diagnosing pregnancy or gynecologic disorders." Further work is required to establish a practical value of this intradermal test.

## CHEMICAL TESTS FOR PREGNANCY

The Urinary Histidine test.

The Visscher-Bowman Test.

The Colorimetric test of Schmulowitz and Wylie.

*The Urinary Histidine Test for Pregnancy.*—Voge[62] using Knoop's bromine water test for histidine, evolved a test for pregnancy based on the finding of histidine, an aminoacid, in the urine of pregnant women. He boiled such urine with dilute bromine water and noted the pink color change. In a series of 60 cases controlled with Aschheim-Zondek test he found this test 95 per cent accurate.

Armstrong and Walker[63] isolated histidine from pregnancy urine and demonstrated that the presence of this aminoacid in the urine accounted for the positive bromine water test of Voge. The exceptionally good results obtained by Voge with so simple a test, stimulated several investigators to study this reaction. Dodds,[64] Siddall and others,[65] and Pellizzari[66] were among the first to repeat this work and irregular results were obtained by each group. Pellizzari found histidine present also in nonpregnant women and declared the test as valueless.

Kapeller-Adler and her associates[67, 68, 69] studied the reaction in great detail, suggested a modification for quantitative histidine determination in urine and claimed excellent results with this new test. In the meantime, Young[70] using the original Voge bromine water test obtained but 63 per cent correct positive reactions and 84 per cent correct negatives. He concluded that this was not a satisfactory test for pregnancy. In 1933 Weisman also used Voge's test and found irregular positive and negative reactions in a series of definitely known late pregnancy cases.[71] Valle,[72] in 1934, used the Kapeller-Adler modified histidine test and found it correct in 98 per cent of his cases, starting at the second month of gestation. Valle performed the test in thirty minutes and his work appeared to be quite promising. Weiss[73] concluded, after investigations into the histidine test, that a definite, positive histidine test was diagnostic of pregnancy. Ohligmacher[74] used the Kapeller-Adler modification of Voge's test and found it no better than the original test! He considered it neither sensitive nor specific. In 1934, Ferrari and Francis[75] of Buenos Aires performed the Kapeller-Adler test and reported it as valueless. However, at about the same time Renton,[76] in South Africa, did 100 tests with the Kapeller-Adler reaction and had only seven false negatives. Brandsch,[77] in Leipzig, found 19 per cent incorrect reactions in early pregnancy and 9 per cent incorrect reactions in late pregnancy. In his opinion the metabolism of histidine is very interesting, though histidine may be present in the urine of nonpregnant females. Foldes[78] obtained poor results with the Kapeller-Adler test but Seidman,[79] in 1935, stated that the histidine test warranted further study because he was not satisfied as to its specificity for pregnancy. Hecksteden[80] maintained that the Kapeller-Adler reaction was useful, reporting 64 correct positives out of 75 cases tested; and 21 correct negatives

out of 26 cases. Though acceptable the Kapeller-Adler reaction was not sufficiently accurate to displace the Aschheim-Zondek test.

In 1936, Gertler[81] demonstrated the presence of histidine in the urine of more than 90 per cent of gravid women, but the reaction often became positive only in the later months of pregnancy. Krieger[82] reviewed the different modifications of the bromine water test, and agreed with Seidman that the histidine test is valueless as a means of detecting early pregnancy. An editorial in the *Journal of the American Medical Association* (June 27, 1936)[83] summarizes: "Further data must be secured in order to determine definitely whether this relatively simple chemical test for urinary histidine may be of at least of some value in the clinical diagnosis of pregnancy."

*The Visscher-Bowman Test.*—Visscher and Bowman,[84] in 1934, devised a new and rather complicated chemical test for pregnancy, which involves the use of many chemical ingredients with a rather muddled and hazy reaction. The original test consisted in the addition of one drop of hydrogen peroxide, five drops of 1 per cent phenylhydrazine-HCl solution in water, five drops of methyl cyanide solution in water, and five drops of concentrated hydrochloric acid to 1 c.c. of urine. The mixture is heated on a water-bath for twenty-five minutes. A russet color and a thick flocculent precipitate denote a strong positive reaction, indicating pregnancy. A brown color and a slight powdery precipitate a doubtful reaction. No color change and no precipitate denotes a negative pregnancy test. Visscher and Bowman reported 93 per cent accuracy in pregnancy cases. In the same year Menken[85] used two different techniques of the test and obtained good results. Later Menken repeated the test on another series[86] and came to the conclusion that a definitely positive test is reliable as proving pregnancy, but that a negative test does not mean the absence of pregnancy. In 1936, Dodds[87] tested 100 cases and obtained a 90 per cent accuracy with pregnant women and 89 per cent exactness with nonpregnant women. Dolff[88] also reported good results with this test, finding the test 94.5 per cent accurate in early pregnancy, and 96 per cent accurate in later pregnancy. However, Dolff found that urines were also positive when they contained excessive amounts of the decomposition products of metabolism. Friedrich[89] stated that the gonad-stimulating hormone is the causative factor and he greatly simplified the Visscher-Bowman technique. Friedrich's technique consists of the simple addition of a few drops of 25 per cent HCl to 1 c.c. of urine which is at the sp. gr. of 1.015. The mixture is heated over a Bunsen burner for two minutes when a color change takes place. A light brown coloration is a negative reaction, and a dark or red brown color is a positive reaction. Friedrich tested 312 cases both with his method and with the original Visscher-Bowman technique. Only five wrong results were obtained with the Visscher-Bowman method, while the hydrochloric acid method of Friedrich gave 100 per cent correct results. Simple addition of HCl to urine certainly would be a convenient indicator of pregnancy. Frech,[90] in 1937, repeated the original Visscher-Bowman test in a series of 513 cases and obtained 92.3 per cent accuracy in diagnosing pregnancies. Frech stated that this test "requires considerable experience in learning to differentiate the various precipitates obtained. It is often difficult to differentiate between a flocculent and a powdery precipitate. The test is positive if a reddish-brown flocculent precipitate is observed;—if straw yellow and the deposit is powdery or absent, it is negative." Frech continues by adding that "in 15 cases checked by Aschheim-Zondek tests only 80 per cent correct results were obtained."

Incidentally, it should be kept in mind that urine contains many substances. John F. Loehle[91] reported very recently that both male and female urines containing sugar, have given a positive Visscher-Bowman reaction. We maintain that any test which is not specific for pregnancy requires particular investigation.

*The Colorimetric Test of Schmulowitz and Wylie.*—In 1935 Schmulowitz and Wylie[92] devised the following pregnancy test: The estrin extracted from urine by

ether is coupled with diazotized para-nitro aniline which gives a color reaction. This color is compared in a colorimeter with a 33 per cent ferric chloride solution. The more intense the estrin color the more hormone is present in the urine. The above investigators have established an arbitrary number above which the pregnancy diagnosis is positive and below which it is negative. They claim excellent results for this test. Pincus and others[93] also advocated a colorimetric method to diagnose pregnancy by estrogens in urine. They varied the Schmulowitz-Wylie test by using phenolsulfonic acid. Pincus and others concluded that the colorimeter test based on estrin in urine is not a reliable test in the early months of pregnancy, but very accurate in the later months of gestation, due to an increase in the urinary estrogen as pregnancy advances.

Realizing the apparent value of the colorimetric test in the last trimester of pregnancy, Savage and Wylie[94] have ingeniously applied the colorimetric test to the diagnosis of toxemias late in pregnancy. In testing nephritic and preeclamptic toxemias of pregnancy they found a diminished amount of estrin in the urine of those cases, with a corresponding "Ferric Number" (F. N.) of low value (ferric number 37-50) while in the normal average pregnancy the ferric number is about 80. However, there is a large percentage of error since 30 per cent of the normal readings are sufficiently low to overlap those of the toxemia readings. This fact warrants further investigation.

## MISCELLANEOUS TESTS FOR PREGNANCY

The following tests are presented purely for the sake of academic interest and completeness. These tests are still in the experimental stages and while some are based on sound physiologic principles, others are simply observations of interesting phenomena.

Hormonal hypercholesterolemia as test for pregnancy
The Bercovitz ophthalmic test
The human vaginal biopsy test for pregnancy
The contractile uterine test of Lorrincz
Pregnancy diagnosis by leucocyte count
The Chamorro-Friedman rabbit test
Infusorial test for pregnancy
Hoffmann seed test for pregnancy
Guinea pig test

*Hormonal Hypercholesterolemia.*—Masciottra and Martinez de Hoz in 1933[95] found that upon injecting pregnant urine into guinea pigs, the cholesterol value increased from 30 to 50 per cent. They considered this a diagnostic test for pregnancy and any increase in cholesterol over 25 per cent was believed to be a positive test. This work was repeated by De Potter[96] but the cholesterol values were found to be so inconsistent, as to be of no clinical value. Gavioli in Buenos Aires[97] also investigated this test and found cholesterol values of no worth in the diagnosis of pregnancy.

*The Bercovitz Ophthalmic Test.*—In 1930 Bercovitz[98] made the observation that a partial mydriosis or myosis would take place in the pupil of a pregnant woman if a few drops of her serum or citrated blood were instilled into the corner of her eyes. This reaction took place in two minutes and according to Bercovitz with 84.7 per cent accuracy. Pouliot used this test and with minor changes in illumination diagnosed 44 cases correctly. Davis, Konikov and Walker used this observation of pupillary changes when performing routine Friedman tests upon rabbits, and could determine the diagnosis of pregnancy by the pupils of the rabbit even before the rabbits were opened for inspection of the ovaries.[99] Their results were 87 per cent correct positives with a 14 per cent error in nonpregnant individuals. There

is no definite explanation for the pupillary change and in many cases of known pregnancy there is neither a dilatation nor a contraction of the pupil. The error in the ophthalmic test is far too great to permit its clinical usage.

*The Human Vaginal Biopsy Test.*—Very recently Smith and Brunner[100] developed a histologic method for the early diagnosis of pregnancy. Sections from vaginal biopsy specimens are studied microscopically. They reported 79 cases; in 26 of them pathologic changes, e.g., due to vaginitis, etc., rendered the specimens useless. The test is therefore hardly a practical one.

*The Contractile Uterine Test.*—Still used by some practitioners in Europe is the test first proposed by Lorrincz, in 1928, and investigated by Reeb in 1932.[101] A sterile solution of posterior pituitary extract is injected into the woman intravenously. The examiner then performs a bimanual palpation. If the woman is pregnant uterine contractions are felt, and in the absence of palpable contractions the patient is considered not pregnant. Reeb advocated this test after diagnosing correctly 5 pregnant and three nonpregnant women, in a series of eight. He cautions against use of this test in late pregnancy but asserts its value in early diagnosis. In my opinion it is too risky for use in any month of pregnancy.

*Pregnancy Diagnosis by Leucocyte Count.*—De Nito[102] recently described a new, rapid method for the early diagnosis of pregnancy. This test is founded on diminution of the leucocytes in the blood of the rabbit after an injection of pregnancy urine. After determination of the rabbit's leucocyte count, 5 to 10 c.c. of urine from the suspected case are injected into the marginal vein of the rabbit's ear. The positive diagnosis of pregnancy depends upon a reduction of leucocytes in from two to four minutes after injection. De Nito obtained in 100 cases a 90 per cent accuracy. The author offers no rationale for the reaction, yet the results and the simplicity of the test warrant further investigation.

*The Chamorro Modification of the Friedman Test.*—Chamorro removed both ovaries from the abdomen of the rabbit and implanted them into the anterior chambers of the same rabbit's eyes. The transplanted ovaries respond in the same manner as ovaries in the Friedman test. The response is slower but available for direct observation. The author performed this test on only a small series of cases and as yet has insufficient data upon which to judge the dependability of such a test.[103]

*Infusorial Test for Pregnancy.*—Kustallow recently used various protozoa in a method for detecting pregnancy.[104] His test consists of the addition of one drop of catheterized urine to one drop of hay infusion containing various protozoa. In case of pregnancy the motion of these organisms is stopped in less than two minutes. Normal urines do not interfere with their movements. Infections of the urinary tract delay the reaction. No percentages of accuracy are given by the author.

*Hoffmann Seed Test.*—Hoffmann[105] found that pregnancy urines inhibit the sprouting of seeds. However, after sprouting has started, pregnancy stimulates the growth much more than normal urine. The results are very vague.

*Guinea Pig Test.*—Gismondi and Acevedo[106] repeated the work of Joel and Andreani Constantin using male guinea pigs one month of age. Two cubic centimeters of pregnancy urine were injected into the heart of the guinea pig and in forty-eight hours hypertrophy of the sexual organs was observed. The results were not found to be reliable.

## SUMMARY

A review of the most recent work in pregnancy testing is presented. The Aschheim-Zondek and Friedman Tests both only seven or eight years old have been established as accepted universal tests for pregnancy. As time passes the slight percentages of error in these tests are growing less and less. Other tests are pre-

sented some of which show promise and others of which are practically worthless. The goal of the investigator is to discover a reliable test for pregnancy which can be performed in a test tube in a few minutes. To that end we can but look to the future.

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# Selected Abstracts

## Complications of Pregnancy With Disease

**Goodall, J. R., and Gottlieb, Rudolf: The Association of Pregnancy, Hypochromic Anemia and Achlorhydria,** Canad. M. A. J. **35:** 50, 1936.

It is known that hypochromic anemia is confined principally to women of middle age and is characterized by pallor, weakness, brittle finger nails, achlorhydria, and an anemia with a lowered hemoglobin content without a corresponding diminution in red blood cells. The onset is insidious.

This series consists of 200 consecutive unselected pregnancies. Only average figures are given. The general average hemoglobin was 75 per cent or 10.5 gm. The first, second, and third trimester averages are 80 per cent (11.2 gm.), 75 per cent (10.5 gm.), and 65 per cent (9.1 gm.), respectively. The red blood cell count shows a decrease for the three trimesters from 4,300,000 to 4,100,000 to 3,700,000, respectively. Only 115 had gastric analyses with 51 per cent, 13 per cent, and 0.5 per cent normal gastric acidity for the respective trimesters. In 85 per cent of the above group acidity began to return within a week postpartum.

There is a definite tendency in pregnancy to the development of a progressive hypochromic anemia and it is more pronounced when the succeeding pregnancies are in rapid order.

The authors feel that the fetus draws upon the maternal source for gastric factor as well as supply of iron. They suggest that the primary cause of hypochromic anemia and its associated lesions is due to an endocrine dysfunction.

Large doses of ferrous carbonate have given satisfying results.

H. CLOSE HESSELTINE.

**Smallwood, W. Carey: The Anaemia of Pregnancy,** Brit. M. J. 2: 573, 1936.

The author presents a classification of the disease based on other recent classifications of blood dyscrasias. He concludes that there exist mild degrees of hypochromic anemia of pregnancy which, though not dangerous to life, are responsible for minor ailments and ill-health in both mother and child and may be prevented or cured by a generous diet and the administration of iron. Occasionally, severe degrees of anemia develop during and as a result of pregnancy in the last trimester.

These conditions require detailed blood studies, accurate diagnosis and prompt treatment directed toward the type of anemia present. A routine hemoglobin estimation at about the seventh month of pregnancy and a detailed hematologic analysis of all cases showing severe degrees of anemia should form part of antenatal supervision.

F. L. Adair and S. A. Pearl.

**Fullerton, Harold W.: Hypochromic Anaemias of Pregnancy and the Puerperium,** Brit. M. J. 2: 577, 1936.

The author presents a study of hypochromic anemia occurring during pregnancy and the puerperium. The average hemoglobin levels of poor women fell during pregnancy up to the thirty-seventh week of gestation then rose slightly before delivery. A rise in hemoglobin level occurred from forty-eight hours postpartum to six to eleven months after delivery. Even in women of poor classes the transfer of iron from the mother to the fetus is compensated wholly or to a large extent by dietary iron. In cases where this demand exceeds the retention of dietary iron, the degree of maternal iron deficiency which results is only slight. Where hypochromic anemia in pregnancy is marked, anemia has probably existed before the pregnancy but has been made more apparent by a physiologic hydremia. Therefore, the conception that uncomplicated pregnancy frequently produces a severe degree of hypochromic anemia should be discarded.

The blood loss during parturition varies greatly in degree and often produces severe hypochromic anemia.

F. L. Adair and S. A. Pearl.

**Moore, Jocelyn, and Pillman-Williams, E. M.: Anaemia and Toxaemia of Pregnancy,** Brit. M. J. 2: 528, 1936.

The authors present a clinical and biochemic study of a group of antenatal patients. Some were treated with iron as a routine throughout pregnancy and others not so treated served as controls.

One patient in the iron-treated group of 35 and 6 patients in the control group of 34 showed degrees of toxemia. Only one case had a toxic albuminuria and blood pressure of 160/90.

The toxic cases showed a rise in hemoglobin under iron therapy. The hemoglobin fell in the control cases before toxic symptoms became apparent. In the nontoxic group of patients the hemoglobin varied from a rise of 17 per cent in iron-treated cases and a fall of 8 per cent in the untreated cases. The iron therapy was associated with an improved general well-being and a reduction in the number of colds, etc. No seasonal variation was noted.

Blood urea studies in these groups are reported as well as results of gastric analysis. Sugar tolerance tests on both groups are described. The results were within normal variations in the latter study, except in the postconfinement curve in the toxic group where the fall was more delayed. In the more toxic patients the sugar curves were more markedly raised coincident with the time of the onset of toxemia and in

the postpartum period. The blood sugar test, therefore, becomes of diagnostic importance. Dietetic treatment in the face of a high blood sugar may serve to divert subsequent disaster.

The authors conclude that the incidence of toxemia was much lower in the iron-treated series than in the controls. When the hemoglobin value is kept up about 90 per cent, the incidence of toxemia is lowered.

F. L. ADAIR AND S. A. PEARL.

**Boycott, John A.: Anaemia in Pregnancy,** Lancet **1**: 1165, 1936.

The author supplies an excellent review of the literature and converts the various results to a common system, thus enabling the reader to follow the comparisons easily. In the study of 222 cases the following technic was employed: hemoglobin estimations are made by the Haldane hemoglobinometer standardized at an oxygen capacity of 18.5 c.cm. per cent, equivalent to 13.8 gm. hemoglobin; red cells are counted by dilution with physiological saline solution in a Bürker chamber; cell diameters are measured by the Price-Jones method; films are fixed and stained in Jenner and counterstained with 0.5 per cent aqueous eosin; and reticulocytes are counted by a wet method.

Anemia is limited to that group having less than 80 per cent hemoglobin.

Evidence is obtained to show that there is an inconsistent increase in the plasma volume in pregnancy causing a dilution of the red cells. Anemias may result from iron deficiency through demands of the fetus and either dietary insufficiency or defective utilization of iron. The other anemias of pregnancy may result from complicating diseases; the majority of these are of the hypochromic type.

Twenty-two per cent of the patients attending the University College Hospital Antenatal Clinic have less than 80 per cent hemoglobin. True anemias may be distinguished from the apparent (dilution) anemias by the blood picture, yet these may coexist. It is stated that anemia is probably not a serious risk in pregnancy in England and that the common anemia of pregnancy responds well to adequate iron treatment unless there is a complicating disease.

H. CLOSE HESSELTINE.

**Bentivoglio, Franco: Chronic Myeloid Leukemia Associated With Pregnancy,** Folia gynaec.-demograph. (Genova) **33**: 53, 1936.

The author briefly describes a case of chronic myeloid leukemia associated with pregnancy and treated by x-ray therapy. During the course of pregnancy there was noted no change for the worse in the leukemia, if anything there was some improvement of the condition.

The pregnancy terminated spontaneously, with the birth of a live child, which had no symptoms of the disease.

MARIO A. CASTALLO.

**Daniachij, M. A.: Pathological Pregnancy and Hematopoiesis,** Zentralbl. f. Gynäk. **60**: 1998, 1936.

Daniachij studied the hematopoiesis of bone marrow in relation to the various pathologic forms of pregnancy with special reference to the toxemias of pregnancy.

In general he found that hematopoiesis in the anemias of pregnancy is markedly suppressed due to the general toxic state of the patient. In studying his case material he found that pregnancy may be considered as being the most important etiologic factor of the various forms of anemia including Edisson-Biermer's pernicious anemia.

Concerning the pathogenesis of these types of anemia, the author found that they are usually associated with very marked toxic changes of the leucoblastic and erythroblastic tissue of the bone marrow which may lead to a complete exhaustion of hematopoietic function. The character and nature of these anemias can only be determined by a careful study of the morphology of the peripheral blood and of the bone marrow.

The author studied furthermore the clinical picture of 20 eclamptic patients in their eighth to tenth month of gestation and found that in eclampsia the bone marrow is involved to the same extent as other parenchymatous organs due to the general toxic state of the patient. The changes observed in the bone marrow are usually edema and fatty degeneration and these pathologic changes involve predominantly the leucoblastic tissue. These changes are of a toxic nature, probably due to the chemical alteration of the body fluids.

It should be noted, however, that degenerative changes in the bone marrow have been found also toward the end of physiologic pregnancies but in these cases they are only slight.

The author believes that these observations are of considerable importance for the study of the pathogenesis of eclampsia.

Daniachij studied also the bone marrow changes in cases of the nephropathies of pregnancy, preeclampsia, albuminuric retinitis and in hyperemesis gravidarum but the case material was not large enough to permit definite conclusions.

RICHARD E. SOMMA.

**Bramwell, Crighton: Treatment of Heart Disease in Pregnancy,** Brit. M. J. **1:** 1132, 1935.

For the choice of treatment the author divides cardiac cases into three groups and considers treatment for each.

In the more serious cases who are known to have had congestive heart failure in the past and in all those with auricular fibrillation, pregnancy should be prohibited, or if present, and the patients are seen in the early stages, the uterus should be emptied. When seen too late for this, they should be kept under close observation, at rest, and when the heart failure is compensated and the child is viable, a cesarean section should be performed. It is especially important to treat the heart failure primarily.

The second group covers patients whose hearts show signs of failure during the last trimester. Pregnancy should be allowed to pursue its normal course under strict medical supervision and rest. In this group cesarean section is favored by the writer. Opinions differ on this point.

The third group comprises trivial cases in whom pregnancy is allowed to pursue its normal course with the provision of adequate antenatal care and hospitalization for delivery.

Avoidance of physical exertion and ample rest and sleep are stressed for all cardiac cases. One whole day in bed each week is advised as a precaution in some patients during the last two months. Sedatives, tonics and diuretics are mentioned, as well as restriction of salt if edema is present. When bronchitis complicates the picture, it should be treated with rest, inhalations, and a stimulating expectorant. Oxygen therapy is useful. Finally the conviction is expressed that proper medical supervision and hospitalization save many a patient who might develop congestive heart failure.

F. L. ADAIR AND S. A. PEARL.

**Donovan, H. C. E.: Heart Disease Complicating Pregnancy,** Brit. M. J. **1:** 104, 1936.

A report of cardiac cases under observation in the antenatal wards of the Women's Hospital, Sydney, is presented. The incidence of heart cases requiring hospital treatment was 0.255 per cent for the graver cases; those with mild or no symptoms are excluded.

Two maternal deaths occurred. One was due to pulmonary embolism following cesarean section. The other, para xiii, showing advanced myocardial degeneration, died from syncope on the day following an easy short labor. Seventeen patients were delivered by cesarean section; 3 had labor induced; 4 had therapeutic abortion by vaginal route, or abdominal hysterotomy. Labor was shortened in most cases of natural labor by forceps at end of second stage.

Mitral stenosis is the commonest lesion. Myocardial degeneration in elderly multiparas is seen; congenital heart disease, aortic stenosis and aortic regurgitation are less common.

Factors deciding treatment are many, i.e., the character of the lesion, the stage of pregnancy, the previous cardiac and obstetric history, the age and parity and the clinical findings and symptoms, as well as the social and economic position. A full history is most important. All factors must be assessed for the individual case. With complete knowledge of the functional capacity of the heart we still have to estimate the strain of labor upon it. We can estimate this by the previous obstetric history, by pelvic measurements, size of the fetus, its presentation and position. Every labor is an experiment in that the expulsive forces and the capacity of the head to mold are unpredictable. A heart with efficient muscular reserve can stand this experiment safely, but a mistaken estimate can kill or cripple for life a heart that is functionally much below normal. Treatment should not be limited to preservation of the maternal life for health should be maintained.

Indications for terminating labor are discussed. Therapeutic abortion is indicated principally in cases which are getting worse in spite of bed rest and digitalis, and in the more severe forms of aortic disease and congenital lesions. Cesarean section should be performed shortly before term on those in whom auricular fibrillation or decompensation occurred in a previous pregnancy. Trial labor, which saves us from so many errors of treatment in dealing with disproportion, has no place in the treatment of heart disease. The lower uterine segment operation is recommended as reducing the purely operative risks of cesarean section.

F. L. Adair and S. A. Pearl.

**Burwell, C. Sidney: The Influence of Pregnancy on the Course of Heart Disease,** South. M. J. **29:** 1194, 1937.

The manifestations of heart disease may remain essentially unchanged over a period of years with the arrest of the primary causative factor (syphilis, rheumatic fever, thyrotoxicosis), and subsequently certain provocative factors not related to the original disease may supervene, and by supplying an extra burden cause symptoms.

These "precipitating factors" or "removable burdens," which are more or less controllable, include pregnancy, excessive exertion, emotional overstrain, severe anemia, infections, marked obesity.

Pregnancy itself, through the circulatory changes that regularly accompany it, imposes upon the heart a burden of increased work that the author compares to the continuous load of valvular disease rather than to the discontinuous load of physical exertion. This extra work is ordinarily well supported by the heart, but additional burdens may tax it to the extent of exceeding the limits of compensation with resulting congestive failure.

Reduction of mortality from heart disease complicated by pregnancy requires that the obstetrician be informed as early as possible of an underlying cardiac disease and that, having evaluated the heart's functional capacity by observing the patient's reaction to moderate physical exertion, he endeavor to control the known and recognized precipitating factors that may superimpose burdens upon a cardiac mechanism that is already taxed with a double load of pregnancy and preexisting heart disease.

ARNOLD GOLDBERGER.

**De Puy, C. A.: Heart Disease Complicating Pregnancy,** Calif. & West. Med. **43:** 355, 1935.

At the Sinai Hospital in Baltimore, cardiac disease was found to be the second most common cause for obstetric deaths. In no class of patients is prenatal care as important as in this class of patients. On the first signs of any unusual symptoms, such as dyspnea, tachycardia, cyanosis, edema or cough, patients are put to bed and kept under observation. If in a reasonable period of time their symptoms do not subside, their pregnancy must be interrupted. If they reestablish their compensation, they may be permitted up and around again with very limited activities. The aid of an internist, interested in heart disease, is almost a necessary adjunct in the care of these patients.

Having successfully passed through pregnancy to term, the next problem is the management of labor. A few days before labor is due, the patient should be hospitalized and put at complete rest. Labor may be induced or allowed to begin spontaneously. When the pains are well established and the cervix has begun to dilate, the patient is given morphin and this is to be repeated as necessary in the first stage. When the cervix is completely dilated and the head is on the perineum, the patient may be given gas and ether by a competent anesthetist, and the delivery completed by forceps. During the third stage of labor, care should be taken to prevent collapse, as the release of the intraabdominal pressure following the strain of labor is apt to cause serious symptoms. Pituitrin should be given, and a tight binder applied to abdomen. The patient should be allowed to rest in the delivery room for one to two hours before being taken to her room.

Cesarean section is not indicated in this class of cases except when there are complications that would require this method of delivery, for other reasons than the heart lesions.

Following her delivery, the cardiac patient should be kept at rest and not allowed up until she is symptom free. She should not be allowed to nurse her baby, as this puts an extra strain upon her. She must take the required amount of rest and avoid overexertion in the care of her baby. At the first sign of a break in her compensation, she should be put to bed.

J. P. GREENHILL.

**Holmgren, B.: Pregnancy and Labor in the Presence of Kyphoscoliosis,** Acta. obst. et gynec. Scandinav. **16:** 267, 1936.

By way of introduction the author gives an account of 259 cases, previously published, of pregnancies in women having a kyphosis. Of these 33 (1/8) died and at least 119 were delivered spontaneously at full term, 11 (1/10) of the latter with fatal issue. Large series with no deaths, published by Lindfors and Klaften show, however, that the death rate of the mother need not be high in cases where an early and careful observation has been made, and the indications have been judiciously considered.

In the author's material, embracing 22 cases of high-grade kyphosis or kyphoscoliosis with 29 observed pregnancies, one death from heart decompensation occurred during pregnancy.

The author makes a comparison with the total number of deliveries and abortions at the General Lying-In Hospital in Stockholm for the same period (50,014 cases), and the result is as follows: spontaneous deliveries at full term occur less frequently in kyphosis (45 per cent as against 75 per cent in the total material), premature labor occurs more frequently (14 per cent as against 6 per cent), deliveries terminated artificially are more frequent in kyphosis (31 as against 6 per cent) and the mortality among viable fetuses is greater (14 as against 4 per cent). The risk of complications in kyphoscoliosis necessitating an operative delivery is consequently greater and the fetal mortality higher. The author's material is too small to allow an estimation of the death risk of the mothers, but the risk does not appear to be remarkably great. There is always a certain risk of cardiac decompensation, which, however, is not as great as has previously been maintained if the patient is kept under medical control.

In a relatively large number of cases showing slight or moderate contraction of the pelvic outlet, the delivery may proceed spontaneously and without complications even though the fetus is fully developed and of normal size.

Owing to the complications to which kyphoscoliotic women are subjected during pregnancy, labor, and the puerperium, the author emphasizes the importance of their being under medical observation as early as possible. Particular regard should be paid to the heart, to the pelvis, and to the vertebral deformity, which if possible should also be examined by x-ray, above all for the purpose of finding out whether a possible tuberculous spondylitis has been healed in a satisfactory manner considering the increased static strain at delivery.

Induced abortion should be resorted to only in the cases which during the first three months of pregnancy show signs of increasing heart decompensation and in cases of tuberculous spondylitis in which the tuberculosis has not yet healed, or has healed in a way so that the pregnancy brings about a statically weakened condition in the spinal column. During decompensation in the latter half of pregnancy an attempt should be made to get the heart compensated by confinement in bed and stimulation in order later on, when the fetus is fully developed, to end the pregnancy if possible by a cesarean section. In case of decompensation during labor the patient should be delivered as soon as possible. Should the fetal head rest on the floor of the pelvis, forceps is the quickest and to the patient, the most indulgent obstetric instrument. In view of the risk of decompensation after labor the patient should be carefully watched during the puerperium.

J. P. GREENHILL.

**Gideon, A.: Difficulties in Pregnant Women Due to Lying on the Back**, Acta obst. et gynec. Scandinav. **15**: 295, 1935.

During the latter half of her first pregnancy a patient previously in good health constantly experiences the following symptoms when lying on her back: marked increase in pulse rate, considerable reduction in blood pressure and pulse pressure and retarded breathing. Roentgenologically reduction of heart volume is demonstrable. Subjectively there is a feeling of discomfort and tension in the upper part of the abdomen, difficulty in breathing, etc.

A series of examinations of patients showed that these symptoms appear only when the pregnant uterus rests against the right, posterior part of the peritoneum.

A survey of the effects of pregnancy on the circulatory apparatus shows that a greatly increased disposition toward circulatory disturbances is present during gestation, particularly in the latter half. Evidence is found in the literature that compression of the vena cava inferior, in experiments on animals, causes reduction of blood pressure and increase of the pulse rate.

The author investigated the symptoms commonly present in gravid women in the dorsal position, and also the spontaneous changes in the sleeping position during the

latter half of pregnancy. Among 653 gravid women, 197 (30 per cent) experienced different symptoms when lying on the back during the latter half of pregnancy (tenderness, fatigue, pains in the abdomen or back, stronger movements of the fetus, palpitation, etc.); forty-two patients (6.4 per cent) could not lie on the back at all. In more than one-third of the patients the sleeping position was changed in the latter part of pregnancy.

The author draws the conclusion that the common symptoms experienced by pregnant women when reclining on the back probably are caused by more or less complete compression of the vena cava by the pregnant uterus, possibly in connection with upward pressure on the diaphragm.

J. P. GREENHILL.

**Pohl, Armin: Thyroid and Pregnancy,** Arch. f. Gynäk. **160**: 447, 1936.

There is a definite and marked increase in size and function of the thyroid during pregnancy. This change is shown by the increase in the minute blood volume of the heart. The typical thyroid of pregnancy can be produced by very small quantities of the thyreotropic hormone of the pituitary. Large doses of pregnancy serum produce definite changes in the thyroid in animal experiments. The author found no evidence of the development of toxic symptoms during pregnancy. A pre-existing Basedow disease becomes worse in only 50 per cent of instances and results fatally in only 6.4 per cent. Some authors claim that the toxic condition is improved by pregnancy.

This increase in thyroid function during pregnancy is not pathologic but is a true work hypertrophy. The other glands are not changed by this action of the thyroid in pregnancy; on the other hand, this change is independent of the function of the other glands of internal secretion.

RALPH A. REIS.

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# Item

## American Board of Obstetrics and Gynecology

The general oral, clinical and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in San Francisco, California, on June 13 and 14, 1938, immediately prior to the meeting of the American Medical Association.

Application for admission to the June, 1938 Group A examinations must be on an official application form and filed in the Secretary's Office before April 1, 1938.

The annual informal Dinner and General Meeting of the Board will be held at the Palace Hotel, San Francisco, on Wednesday evening, June 15, 1938, at seven o'clock. Dr. William D. Cutter, Secretary of the Council on Medical Education and Hospitals of the American Medical Association will be the guest speaker, and the Diplomates certified at the preceding days' examinations will be introduced individually. All Diplomates are invited to attend the dinner meeting, and to bring as guests their wives and any persons interested in the work of the Board.

For further information and application blanks address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pa.

# Books Received

OPERATIVE OBSTETRICS. By J. M. Munro Kerr. Emeritus Regius Professor of Midwifery, University of Glasgow, etc. Fourth edition with the assistance of Donald McIntyre, Consulting Obstetric Surgeon, Brashaw Maternity Hospital, etc., and D. Fyfe Anderson, Senior Assistant Professor of Obstetrics and Gynaecology, Glasgow University, etc. With 338 illustrations in the text, 847 pages, William Wood and Company, Baltimore, 1937.

ANNUAL REPORT ON THE RESULTS OF RADIOTHERAPY in Cancer of the Uterine Cervix. First volume: Results obtained in 1930 and previous years. Edited by J. Heyman, M.D., Stockholm. League of Nations Health Organization. Columbia University Press, New York, 1937.

THE BABY'S FIRST TWO YEARS. By Richard M. Smith, Assistant Professor of Pediatrics and Child Hygiene, Harvard Medical School and School of Public Health, etc. With illustrations, 121 pages. New and revised edition. Houghton Mifflin Company, Boston, 1937.

GENITAL ABNORMALITIES, HERMAPHRODITISM AND RELATED ADRENAL DISEASES. By Hugh Hampton Young, Professor of Urology, Johns Hopkins University, etc. With 379 plates, containing 534 drawings by William P. Didusch, 649 pages. Williams and Wilkins Company, Baltimore, 1937.

THE DIARY OF A SURGEON in the year 1751-1752. By John Knyveton, edited by Ernest Gray. 322 pages. D. Appleton-Century Co. New York, 1937.

INSUFFLATION TUBAIRE KYMOGRAPHIQUE par la méthode de Rubin. Par Louis Bonnet, ancien chef de clinique gynécologique à la Faculté de Médecine de Paris. Avec figures, 96 pages. G. Doin & Cie, Paris, 1937.

LEUCOPLASIA DE LA VULVA. Par Dr. Pedro Figueroa Casas, Professor Adjunto de Clinica Ginecológica de la Facultad de Ciencias Médicas de Rosario, etc. Liberia y editorial Ruiz, Rosario, 1937.

PHYSICAL DIAGNOSIS. By Don C. Sutton, Associate Professor of Medicine, Northwestern University School of Medicine, etc. With 298 text illustrations and 8 color plates, 495 pages. The C. V. Mosby Company, St. Louis, 1937.

TEXTBOOK OF DIAGNOSTIC ROENTGENOLOGY. By Lewis J. Friedmann, M.D., Director of Roentgen Ray Department, Bellevue Hospital, etc. With 638 illustrations, 622 pages. D. Appleton-Century Co., Inc., New York, 1937.

MALADIES DES FEMMES ENCEINTES. Tome III. Affections de la Peau. Par Henri Vignes, avec la collaboration de F. Hanoun et G. Vial. 202 pages. Masson & Cie, éditeurs, Paris, 1937.

SYNOPSIS OF ANO-RECTAL DISEASES. By Louis J. Hirschmann, Professor of Proctology, Wayne University, etc. With 174 text illustrations and 6 color plates, 288 pages. The C. V. Mosby Co., St. Louis, 1937.

PRENATAL AND POSTNATAL MANAGEMENT. By J. St. George Wilson, Hon. Obstetric and Gynaecological Surgeon, Royal Infirmary, Liverpool, etc. With a foreword by Sir Comyns Berkeley. With 80 figures and a color plate, 206 pages. William Wood & Co., Baltimore, 1937.

PROPEDEUTICA OBSTETRICA. Prof. Arnoldo de Moraes, Professor Cathedratico de Clinica Gynecologica da Faculdade Nacional de Medicina da Universidade do Brasil. 5. Edicao. Com 490 paginas e 158 gravuras. Grafica Suer, Rio de Janeiro, 1937.

THE THERAPEUTIC PROBLEM IN BOWEL OBSTRUCTIONS. By Owen H. Wangensteen, M.D., Ph.D., Professor of Surgery, University of Minnesota, etc. Ninety illustrations, 360 pages. Charles C. Thomas, Springfield, Ill., 1937.